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# RED MEAT IN HUMAN EVOLUTION, HEALTH, AND DISEASE: FROM A BLESSING TO A CURSE?

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ABSTRACT
*Paleoanthropological data, such as butchery tools in the archeological record and cut marks on animal fossils, indicate that access to animal tissues likely predated the emergence of the genus* Homo, *and that its consumption likely increased during expansion of the human lineage. "Red meat" most commonly refers to muscle tissue from large domestic mammals. The red color reflects its rich content of heme iron associated with myoglobin. Given the high nutritive value of animal-sourced foods—rich in iron, zinc, and B vitamins, and fatty tissues providing essential lipids and calories—these resources are especially important during pregnancy, lactation, weaning, and early childhood. Access to red meat and related foods thus likely shaped the evolution of our species. However, in modern contexts, overreliance on red meat—at the expense of dietary diversity from plant fibers—is associated with chronic diseases such as cancer, atherosclerosis, obesity, and type 2 diabetes. Given that red meat is now sought after in most societies, its increasing large-scale production contributes substantially to environmental degradation and climate change. Here, we examine information spanning approximately 3 million years, discussing how so-called "red meat"—once a valuable resource—has, in modern times, been transformed from a "blessing" to a "curse."*

## INTRODUCTION

THE contemporary global appetite for red meat has deep evolutionary roots, as the incorporation of meat into the early hominin diet has long been presumed to have been a watershed event for the evolution of our lineage (Stiner 1993; Domínguez-Rodrigo and Pickering 2017; Thompson et al. 2019).

In its most accessible form, red meat (defined below) is as common as the ubiquitous fast food hamburger found in nearly every major metropolitan area; or, in its most exclusive form, manifesting as "exquisite" Kobe

or Wagyu beef steak in premier dining venues (Motoyama et al. 2016). Worldwide production, processing, transport, and consumption of meat is at an all-time high, driven by a rise in both per-person consumption and total number of consumers, particularly in middle- and high-income countries (Godfray et al. 2018). The global meat industry, comprising a small group of dominant meat production and packing companies, is fulfilling this demand by intensive production and massive intercontinental shipping. These companies collectively held a value of $1.3 trillion (U.S.) in 2021, and it is projected that their worth will increase to $1.6 trillion by 2028 (International Market Analysis Research and Consulting Group 2023), almost rivaling the value of the global automobile market (estimated at approximately $2.86 trillion; Statista 2023). In recent times, international bovine meat prices—the highest among all red meats—rose further with herd rebuilding, driven by an unrelenting consumer appetite for beef (Food and Agriculture Organization of the United Nations 2022).

Humans—the primate species with the most flexible dietary niche, and the world's only living "cucinivore" (a species that cooks its food)—consume a wide variety of adaptive diets shaped by both ecology and culture (Wrangham 2009). In addition to cooking, humans rely on complex food-processing methods, such as grinding, pounding, soaking, winnowing, and fermenting, which are widespread among hunter-gatherer societies and rooted in deep-time culinary traditions (Crittenden and Schnorr 2017). Dietary flexibility characterized much of our hominin lineage and, to a much lesser extent, our closest living relatives, bonobos and chimpanzees (Ungar 2007; Sayers and Lovejoy 2014). Still, a central question remains: to what extent did meat consumption shape human evolution?

For over a century, anthropologists have emphasized meat consumption as a catalyst for key transitions in human evolution, including tool use, pair bonding, provisioning, brain expansion, cooperation, and increased longevity (Washburn et al. 1968; Lovejoy 1981; Rose and Marshall 1996; Stanford and Bunn 2001). However, red meat's prominence in this story may reflect more about what survives archeologically than what was most consumed. Animal bones, especially those bearing cut marks, and the stone tools used to process them, preserve far better than most plant materials, including nuts and underground storage organs (tubers). In reconstructions of ancestral diets, this preservation bias risks overstating the nutritional role of red meat while underrepresenting the contributions of plant-based foods, often provided and processed by women and older children (Kramer 2023).

The term "red meat" can be misleading in the context of ancestral diets. Although there is broad consensus that animal-sourced tissues—such as bone marrow, fat deposits, and brain and other fat-rich organs—were valuable, especially in resource-scarce or seasonal environments (Plummer et al. 2023), lean muscle was not necessarily the primary target of early hunters. Ethnographic and archeological evidence suggests that fatty tissues were the most sought-after parts of animal carcasses, valued for their caloric density, metabolic efficiency, and value for infant brain development during weaning (Speth 2010; Thompson et al. 2019). In contrast, muscle meat, often praised today for being "lean," is metabolically expensive to process and low in usable energy to fuel a growing brain (Speth 2010). It may have been dried and stored as a fallback food or consumed in combination with fat or carbohydrate sources, rather than prioritized as a standalone dietary staple (Speth 2022a). The cultural prominence of red meat in modern Euro-American diets, typically centered on steaks and roasts, reflects ideals and biases that influence assumptions about early hominin diets.

Although hunting likely held profound social and symbolic value, its nutritional contribution across millions of years of evolution remains hard to quantify. The frequency and volume of meat intake among early hominins are unknown, with data limited to marked bones scattered across vast geographic and temporal spans. Despite such limitations, we suggest that the consumption of red meat may have been a "blessing" to early humans

and should be considered, along with other animal foods, as a key component of a broader, flexible dietary niche that also included diverse plant-based resources and culinary innovations.

Although protein consumption was undoubtedly essential for human health and reproductive success, protein needs could have been met through a combination of nuts, eggs, insects, small vertebrates, aquatic invertebrates, fish, and other gathered plant foods, none of which alone would have been strictly "vital." Evidence from modern-day foragers—such as the Hadza, San, and Aché—suggests that hunting large game is often inefficient and frequently unsuccessful, even with the aid of advanced tools, weapons, and arrow poisons (Lee 1979; Hawkes et al. 1991; Hill and Hurtado 1996; Wood and Marlowe 2013). Despite modern cognitive abilities and advanced hunting technologies, success rates among living forager groups remain low, illuminating just how energetically costly and unreliable large-game hunting can be. Yet, when successful, large-bodied animals offered not only meat but also prized fat, nutrient-dense organs, and other useful animal materials (e.g., hides, tendons, teeth, and bones). Today, the overconsumption and overproduction of red meat are increasingly linked to numerous chronic diseases and large-scale environmental impacts, a consequence perhaps unsurprising given the annual raising, slaughtering, processing, and transport of over 1.5 billion pigs, 574 million sheep, 479 million goats, and 302 million cattle (Ritchie et al. 2017; Orzechowski 2022). Environmentally, large-scale animal husbandry requires wide swaths of land, pollutes freshwater and soil sources with hazardous livestock waste and chemical byproducts (Godfray et al. 2018), and leads to extensive deforestation. Over 60% of the Brazilian Amazon has been cleared for cattle farming this century alone (Tyukavina et al. 2017). These land-use changes contribute to and occur amid the backdrop of the climate change crisis, primarily driven by anthropogenic factors. One of the major factors is the industrialization of meat production (Godfray et al. 2018), a rapidly growing sector generating approximately 15% of all greenhouse gas (GHG) emissions, carbon dioxide ($CO_2$), methane ($CH_4$), and nitrous oxide ($N_2O$) that results in and exacerbates the occurrence and severity of extreme weather events: flooding and/or droughts that, in turn, give rise to disparate but interconnected challenges—from food safety and distribution issues locally to smog and air pollution-induced respiratory diseases globally (Domingo et al. 2021).

As the global population approaches 10 billion by midcentury and dietary patterns shift further toward increased meat intake, worldwide emissions from livestock production will only rise. Based on one estimate, the consumption of meat from ruminant animals such as cattle is projected to increase 90% by 2050, while the consumption of all animal products is expected to climb as much as 70% (Sans and Combris 2015). Even if all non-food system emissions ceased, present trends indicate that emissions from this sector will likely surpass the 1.5°C global warming threshold (Clark et al. 2020). Notably, the rearing of cattle alone is expected to account for more than one-half of the future warming associated with the food system; hence, if business-as-usual food production and consumption patterns persist, GHG emissions from meat production will remain one of the biggest contributors to global warming and climate change by the close of the century (Ivanovich et al. 2023).

Here, we provide a panoramic view of red meat as a food source, including anatomical and physiological changes associated with an evolutionary shift to a more energy-dense and diverse diet. We also discuss the nutritional benefits and adaptations it likely conferred during critical life stages. These data are then contextualized by a discussion of contemporary trends in red meat consumption, and its chronic disease-related risks, along with proposed mechanisms by which excess red meat intake may contribute to adverse health outcomes. The environmental impacts associated with mass animal production will also be featured given their direct and lasting public health consequences. Our aim is to provide a broad review of the role that red meat played in the diets of our earliest ancestors and to argue that this one specific food source, once a key "blessing"

during human evolution, now has ominous implications—a potential "curse" posing serious threats to both human health and planetary ecology in the 21st century.

## Meat Definitions and Associated Health Risks

Although most nutritional anthropologists, dietitians, and food historians agree that meat has historic, social, and environmental consequences (Bohm et al. 2015; Leroy and Praet 2015), the definition of *red meat* remains somewhat vague across disciplines. For example, the European Commission defines "meat" as the edible parts of the carcass of domesticated ungulates (bovine, porcine, ovine, and caprine animals), equids (horses), poultry, lagomorphs (rabbits), and miscellaneous wild game. However, what counts as "edible" is left largely undefined. In many industrialized food systems, this usually refers to skeletal muscle and select organs, whereas in diverse small-scale hunting traditions, "edible" often includes the parts discarded in commercial markets—eyeballs, brains, testicles, adrenal glands, spleen, bile, and even rumen and amniotic fluids. This inconsistency further complicates efforts to clearly define "meat," especially across cultures and time periods, and suggests that the modern term inherently reflects cultural preferences more than biological or ecological boundaries. Although the European Commission emphasizes domesticated species and terrestrial game, many cultures—past and present—would also include aquatic, avian, amphibian, or riparian game within their conception of "meat." This ambiguity reflects not only regulatory inconsistencies but also profound cultural differences in what is considered consumable animal matter.

The distinction between "red" and "white" meat can also be ambiguous and variable. Nutritionally, red meat is characterized by higher myoglobin content, the oxygen-binding protein responsible for the red color in muscle meat (U.S. Department of Agriculture Food Safety and Inspection Service 2013). Poultry and fish, both categorized as white meats, contain much less myoglobin than red meats such as beef, pork, lamb, veal, mutton, goat, and horse (Fletcher 2002). In nutritional epidemiology, red meat is defined as *unprocessed mammalian muscle meat*, including minced or frozen forms of these meats, typically consumed cooked (Bouvard et al. 2015). For clarity and consistency, we adopt this epidemiological definition when evaluating chronic disease risk in contemporary industrialized societies that favor skeletal muscle cuts from cows, pigs, sheep, and the like. Processed mammalian muscle meat, by contrast, includes meats transformed through salting, smoking, tenderizing, pickling, enzymatic treatment, and/or addition of preservatives, including curing with nitrites. Many processed meats are made from cows and pigs, but processed products can also include poultry and other meat byproducts (e.g., liver or blood) that have been cured, smoked, or fermented.

We emphasize that this is a highly constrained subset of what was consumed historically. In many ancestral (and traditional) human diets, *meat* encompassed a far broader spectrum of animal-derived tissues: organs, marrow, brain, blood, and other soft parts from both terrestrial and aquatic species. These were eaten raw, cooked, or spoiled, and could have contained insect larvae. Such diets also tended to follow markedly different eating rhythms, alternating between episodes of extreme caloric intake and one or more days with little or no food, a form of intermittent fasting common among foraging peoples. These patterns likely produced distinct metabolic adaptations to irregular, fat-rich diets, quite unlike those of modern populations consuming regular meals centered on lean, red meats. In many traditional contexts, skeletal muscle meat may have been less prized than nutrient-rich tissues like brain or bone marrow. Thus, assessing the health impacts of red meat across human history is a context-dependent endeavor.

In this review, we focus on the dominant form of red meat most commonly consumed in Western diets today: cooked skeletal muscle from domesticated mammals, stripped of organs, and mass produced. This definition allows us to engage directly in discussions about red meat's role in health and disease. However, despite only sharing a superficial

resemblance to the diverse and complex animal foods consumed by our ancestors, modern red meat consumption is frequently justified as ancestral in everyday dietary guidelines, popular discourse, and social media. Conflating these distinct dietary compositions risks obscuring key nutritional, metabolic, cultural, environmental, and public health factors that fundamentally impact human health.

## The Role of Animal-Derived Foods in Human Evolution

A variety of different habitats characterized much of eastern Africa as early as the Miocene epoch (approximately 23 to 5 mya), including an expansion of grasslands and the proliferation and evolutionary radiation of grass-eating, ruminant ungulates across much of eastern and southern Africa (Peppe et al. 2023), ecosystems that are far richer in megavertebrates than any forested habitats. Beginning in the early to middle Pliocene (5.3 to approximately 2.6 mya), associated faunal and stable carbon isotope evidence indicate the presence of early hominins, likely venturing out into woodland (White et al. 2009a, b), savanna woodland (Nishida et al. 1992) and, possibly, more open savanna habitats (Constantino and Wood 2004), a time corresponding to the emergence of striding bipedalism and the capacity for endurance running, presumed to be associated with loss (or rather miniaturization) of body hair and evolution of a much higher density of eccrine sweat glands in our lineage (DeSilva 2021).

Available food sources differed greatly from those eaten by Miocene and Pliocene ape species (a group poorly represented in the fossil record) who lived in closed canopy forests and woodlands (Green et al. 2022). The presence of hominins in more open habitats during the Pliocene led to suggestions that our lineage is a product of $C_4$ plant carbon fixation (a derived form of photosynthesis adapted to hotter and drier habitats) or a world dominated by tropical grasses (Cerling 1992) and/or possibly sedges (Sponheimer et al. 2005). More recent analyses suggest greater complexity in nutritional strategies of early hominins (Sponheimer et al. 2023; Teaford et al. 2023). This complexity reflects a flexibility that emphasizes the need to integrate multiple lines of evidence (including isotopic, morphological, and ecological data) to better reconstruct the dietary landscapes that shaped our evolutionary history.

Beginning in the middle Pliocene or earlier, hominins began consuming animal tissues from prey larger than themselves—a behavior not observed in any other primate—even though such large animals likely did not provide the majority of their daily calories (Stanford 1999). During the mid-to-late Pliocene, increases in hominin brain size coincided with technological innovations in stone tools, which is presumed to have facilitated greater access to large and small animal-derived foods (Elton et al. 2001; DeSilva et al. 2021). These archeological correlations have come to be interpreted through a protein-centric lens, in which access to animal protein, particularly from large game, was theorized to have fueled anatomical and cognitive changes (see below). This framing gained traction for several reasons, although each is problematic.

As others have pointed out, protein is neither energy-dense (providing approximately 4 kcal/g before accounting for the energetic cost of metabolism) nor an optimal primary fuel for the developing brain, which relies predominantly on glucose and ketone bodies (Speth and Spielmann 1983; Speth 2010, 2025). Raw muscle meat is also less digestible without cooking or putrefaction, whereas early hominins likely secured more energy-dense resources—fat from marrow, brain, and other organs—alongside carbohydrate-dense staples such as tubers and honey (Pennisi 1999; Crittenden 2011; Marlowe et al. 2014). These foods would have complemented protein intake and supported a higher-quality diet without exclusive reliance on cooked muscle meat. Some have proposed that diverse animal foods may have enabled females to produce infants with larger brains than their predecessors (Martin 1996; Du et al. 2018) and/or reduced hindgut size, freeing energy for brain enlargement (Aiello and Wheeler 1995). Although muscle tissue is protein-rich, human breast milk contains exceptionally little protein compared to that of many other mammals (Bounous et al. 1988), and the unusually high fat reserves of human infants (among

the highest in the animal kingdom) point to a greater demand for lipid-rich, energy-dense foods in early life (Kuzawa 1998; Cunnane and Crawford 2003).

Notwithstanding ongoing debates over the amount, frequency, and type of animal tissues consumed by early hominins (e.g., outside versus inside of bones; Speth 1989, 2010; Thompson et al. 2019), this dietary shift occurred alongside major anatomical changes: increases in overall body size to near-modern human proportions; reduced sexual dimorphism; smaller premolars and molars; decreased masticatory musculature; increased cranial volume; less robust cranial and jaw morphology; adaptations for endurance running; and aimed throwing. Changes in gastrointestinal (GI) morphology were also profound (Pennisi 1999; Wrangham and Conklin-Brittain 2003; Marlowe et al. 2014; Hardy et al. 2015; Amato et al. 2021). In *Homo sapiens*, the colon comprises approximately 20% of total GI volume compared with approximately 50% in "great apes" (e.g., chimpanzees, bonobos, gorillas, and orangutans; Milton and Demment 1988; Milton 2003), indicating a reduced reliance on microbial fermentation of plant matter and a shift toward foods—animal or plant parts—that are more easily digested and energy-dense (Popovich et al. 1997). The significant size of the large-bodied ape colon is what allows for the fermentation of "low-quality" plant fibers, allowing for the microbially derived digestion of complex polysaccharides and their conversion to short-chain fatty acids (Leonard et al. 2007), the main byproducts of hindgut fermentation.

It appears that the inclusion of an expanding animal-derived food niche in ancestral diets—ranging from red meat, marrow, brain, and other fats to insects, larvae, eggs, aquatic animals, and possibly amphibians and reptiles—offered concentrated and variable sources of essential macro- and micronutrients that were absorbed further "upstream" in the GI tract, in contrast to the great apes' heavier reliance on hindgut fermentation of fibrous plant foods. These foods, along with energy-rich plant resources such as nuts, seeds, tubers, and certain fruits likely marked a fundamental dietary shift associated with ecological, physical, and behavioral changes throughout human evolution (Milton 1999a). Regardless of the specific animal or method of acquisition (hunting versus scavenging; Bunn and Ezzo 1993), most interpretations of hominin dietary evolution suggest a gradual transition from an almost exclusively plant-based diet in the early Pliocene to one that increasingly incorporated diverse animal tissues by the end of the Pliocene (Washburn et al. 1968; Crittenden 2011; Wrangham 2011; McGrew 2014; Thompson et al. 2019). Apart from tarsiers of Southeast Asia, which are exclusive insect eaters, virtually all other nonhuman primates are dependent on predominately plant-based foods (Dudley 2000; Wolf 2002; Potts 2004; Gómez and Verdú 2012; Schoeninger 2014). Great apes today consume mostly fruit- and plant-heavy foods, supplemented occasionally with invertebrates and small vertebrates (Hardus et al. 2012; Hamad et al. 2014; Marlowe et al. 2014; McGrew 2014; Tennie et al. 2014). Humans, among all living great apes, have the most reduced cecum size (Scott 1980). However, the absence of soft-tissue evidence in extinct hominins precludes determination of when GI anatomy began to differ from that of other apes, nor can we confidently link early hominin meat consumption to these anatomic changes.

What is known is that hominids retain analogous GI morphology, characterized by a simple acidified stomach, small intestine, cecum, appendix, and colon. Despite these gross similarities, a striking reduction in the size of the colon and an enlargement of the small intestine are key differences between the human digestive tract from that of other related primates (Milton 1986; Aiello and Wheeler 1995; Lambert 1998). The ape hindgut evolved to process the abundant fibrous plant materials, such as pectin, cellulose, hemicellulose, and other polysaccharides, largely through microbial fermentation. In contrast, humans have a relatively larger small intestine, suggesting adaptation to a diet of greater diversity and nutritional density (Milton 1999b; Furness and Bravo 2015; Figure 1). This shift is often implicitly tied to hominin use of fire and cooking, practices that can enhance nutrient availability, although such connections remain speculative given the ongoing debate over when controlled fire use became widespread

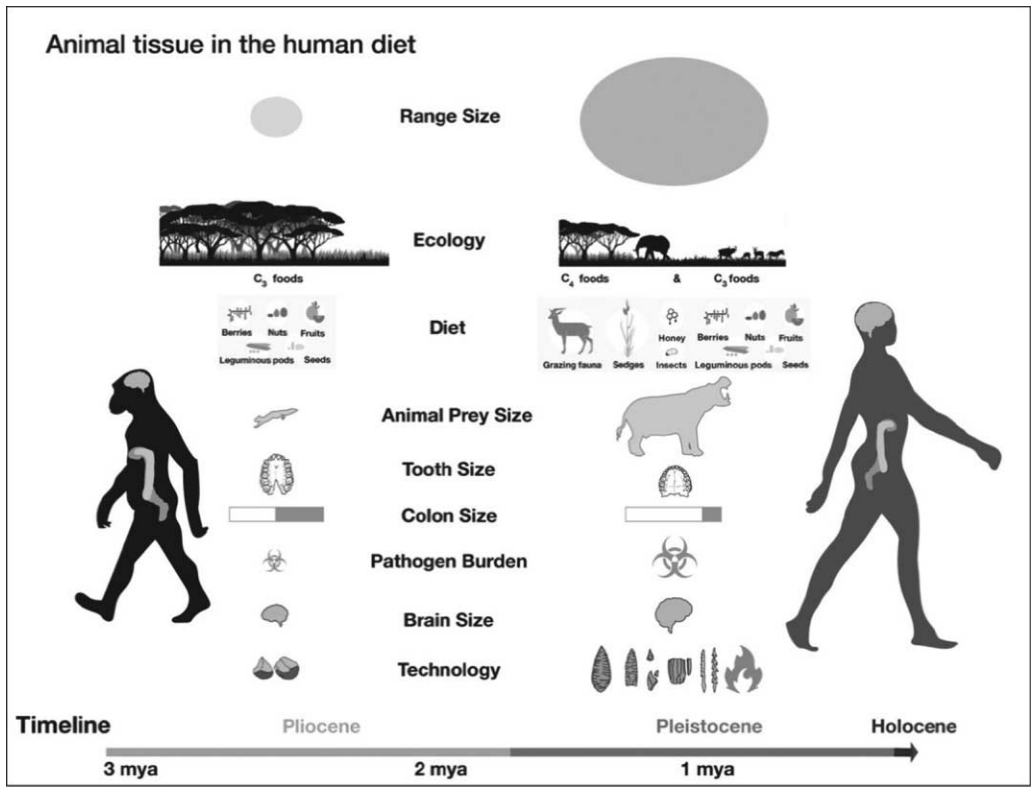


FIGURE 1. ANIMAL TISSUES IN THE HUMAN DIET

As *Homo sapiens* increasingly relied on animal-derived foods—whether hunted or scavenged from large mammals—the diet expanded to include "red meat" (muscle meat), fat-rich organs, and nutrient-dense bone marrow. Efficient bipedality, advanced toolmaking, and complex social systems enabled our lineage to become top predators, range across greater distances, transport and share animal tissues (especially from ruminants in grassland ecosystems), and use fire and other processing methods to extract life-supporting nutrients. These shifts reshaped human biology in profound ways: altering energetic budgets, restructuring the GI tract, supporting larger brains, and reducing the demands on dentition and mastication. They also influenced the pathogen exposure of our ancestors (Bryant et al. 2023).

(James et al. 1989; Goren-Inbar et al. 2004; Hlubik et al. 2019). If regular cooking did not emerge until less than 500,000 years ago (500 ka), its relevance to earlier dietary shifts becomes questionable—particularly since raw muscle meat is neither especially digestible without cooking or putrefaction, nor an optimal primary fuel for the developing brain. Greater nutrient availability, therefore, need not imply a singular focus on meat or cooking. It could have been achieved through multiple complementary strategies independent of animal foods, such as mechanical processing (e.g., pounding, grinding) and soaking of plant materials. Even without cooking, microbial fermentation and putrefaction can break down complex tissues in ways that mimic some of its effects, underscoring that nutrient-dense diets could have emerged through multiple pathways well before regular fire use or the roasting of nutrient-dense meat.

It seems reasonable that simultaneous access to and acquisition of plant foods—such as leaves, fruits, vegetables, nuts, and seeds—and a variety of animal-derived products—particularly vertebrate fat, marrow, and other calorically dense organs, insects, larvae, eggs, aquatic animals, and possibly amphibians and reptiles—may have collectively represented, for the first time in hominin evolution, an abundance of highly bioavailable

nutrients. These encompassed fatty acids, all essential amino acids, B vitamins, and most minerals, such as iron (Millward 1999). One influential model—the *expensive tissue hypothesis*—theorized that early hominins could reduce the size and energy cost of gut tissue, reallocating the saved energy to other organs, most notably the brain, by meeting their nutrient needs through a broad range of animal foods (Aiello and Wheeler 1995). This hypothesis links GI anatomy to diet quality, implying that a smaller colon reflects a shift toward more easily digestible, nutrient-dense foods such as red meat. In this view, some animal-derived components may have facilitated neural expansion while reducing the gut's energy demands. The concept that physiological limitations lead to tradeoffs between one metabolically demanding tissue and another implicitly suggests that investments in these tissues should display a negative correlation. Although this theory has been widely cited, comparative analyses of relative tissue investments across mammals have yielded a range of results, from the anticipated negative correlations (Aiello and Wheeler 1995; Kaufman 2003; Pitnick et al. 2006; Navarrete et al. 2011) to conflicting positive correlations (Jones and MacLarnon 2004; Bordes et al. 2011; Navarrete et al. 2011). Comparative studies do not support the expensive tissue hypothesis (Isler and van Schaik 2006; Schillaci 2006; Lemaître et al. 2009; Barrickman and Lin 2010; Navarrete et al. 2011).

Meanwhile, the *cooking hypothesis* proposes that it was the controlled use of fire for cooking that provided the consequential distinction that came to define the genus *Homo*. Thermal processing of food critically improves digestibility of plants, such as certain fibers, thereby enhancing the efficiency of fermentation and digestion processes in the GI tract (Teaford and Ungar 2000; Carmody et al. 2011). Thermal processing not only reduces the effort and time required for chewing but also deactivates the many antinutritional factors by transforming toxic proteins like lectins and protease inhibitors, present in many raw seeds and tubers, into innocuous and nutritious proteins (Greenhouse 1981; Glander 1982; Wrangham 2009). Furthermore, cooking gelatinizes starches and renders red meat easier to chew and much more digestible. The cooking hypothesis argues that cooking reduced the time and energy required for all-day foraging, chewing, and digesting, allowing those "saved calories" to be redirected toward metabolically expensive tissues such as the brain and a larger body. Although compelling for more recent stages of human evolution, this hypothesis often neglects other forms of complex food processing (e.g., fermenting, winnowing, or pounding) that likely had relevance in early dietary strategies. Moreover, conclusive archeological evidence for fire use by *Australopithecus* species or early *Homo* remains absent, and most purported finds from Plio-Pleistocene sites are still contested. The earliest widely accepted evidence for controlled fire use is associated with *Homo erectus*, often cited at approximately 1.5 mya during the Middle Pleistocene (Hlubik et al. 2019). Another estimate for the controlled use of fire is around 790 ka (Goren-Inbar et al. 2004), but the oldest agreed upon date for the confirmation of hearths (firepits or other fireplace features) can be attributed to *Homo heidelbergensis*, around 250 ka in Eurasia (James et al. 1989). Still, the evidence indicating mastery of fire in the Lower Pleistocene places this behavior after the rise of *H. erectus* (Goren-Inbar et al. 2004), which is long after observed cranial volume expansion, dental size reduction, and reduced masticatory muscles and chewing force (Eng et al. 2013). The true origin of *Homo*-controlled fire use must precede even the earliest archeological evidence of its use. Although we may never know the true age of controlled fire for the specific use of cooking plant- and animal-based foods, a connection between neural expansion and meat consumption is commonly proposed in paleoanthropological or archeological literature.

Achieving mastery of fire, cooking, and toolmaking for hunting would appear to require cognitive capacities for planning, coordinated, and sustained effort. Such considerations challenge the traditional emphasis on hunting and skeletal muscle meat and suggests alternative explanations for how early hominins met their nutritional needs.

In this context, the *external fermentation hypothesis* offers another angle by proposing that cultural food processing—externalizing part of digestion through practices such as fermentation—may have reduced the body's energetic demands and contributed to the energy surplus required for brain expansion (Bryant et al. 2023). This hypothesis builds on the concept that controlled chemical breakdown of food—using naturally occurring bacteria, yeasts, or other microorganisms to transform it—enhances macronutrient digestibility and preservation, effectively a form of predigestion (Rogers and Whittier 1928; Janzen 1977; Thomson et al. 2005). External fermentation further enhances the nutritional quality of food by critically increasing the content of free amino acids (Gobbetti et al. 1994) and essential vitamins (National Research Council 1996; LeBlanc et al. 2013; Tamang et al. 2016). However, evidence supporting this hypothesis is limited. Furthermore, many well-studied foraging societies do not use fermentation regularly or at all. The Hadza, for example, do not intentionally ferment their meat, but they may on occasion consume putrid or decomposed meat when discovered (J. O'Connell, pers. comm.). Given the rapid decomposition of carcasses in sub-Saharan Africa, early hominins opportunistically scavenging meat would have encountered this inevitable putrefaction automatically. However, the living great apes very rarely scavenge (Baker et al. 2024).

Humans relying exclusively on lean animal meats risk a debilitating and potentially life-threatening condition known as "rabbit starvation," also called "caribou sickness" (*mal de caribou*) or protein poisoning (Stefansson 1939). This occurs when protein intake exceeds the liver's capacity to safely metabolize and excrete excess nitrogen, typically somewhere above 250 to 300 grams per day (Speth 2025), depending on body weight (Bilsborough and Mann 2006), and results in symptoms such as weakness, fatigue, nausea, and diarrhea. This reflects a metabolic toxicity rather than a mere nutritional imbalance from the meat itself. The rarity of protein toxicity in many environments, including sub-Saharan Africa, could indicate that early humans incorporated fats, organs, insects, and novel food processing methods—diverse and regional adaptations that likely shaped human nutrition long before the mastery of controlled fire. Recent evidence from Olduvai indicates that some animal prey or plant foods may have been "cooked" by immersion into geothermal hot springs (Sistiaga et al. 2020).

## Paleoanthropological Evidence of Meat Eating

Advances in paleoanthropology and bioarcheology over the past several decades have expanded our understanding of the potential place of red meat within the diets of early hominins. Evidence comes from stone tools, cut marks on animal bones, stable isotope analyses, dental microwear, and plant residues such as phytoliths and starch grains preserved in dental calculus. Each line of evidence is, however, open to debate and alternative interpretation. For example, although stone tools appear in the record as early as approximately 3.3 mya (McPherron et al. 2010; Harmand et al. 2015), their specific uses are difficult to assess. The recent discovery of Oldowan tools alongside hippopotamid bones at two approximately 3-million-year-old sites suggests access to mammalian meat (Plummer et al. 2023), but spatial association alone does not confirm a butchery function or a reliance on skeletal muscle tissue. Other studies indicate that early tools were also used to process fibrous plant materials (Lemorini et al. 2014) and to extract insect resources, especially beehives (Crittenden 2011), although doing so would have required the control of fire for smoking. Lastly, use-wear analysis is commonly constrained by surface weathering and the coarse grain of many lithic materials, leaving much about Oldowan tool functions unresolved.

Given these uncertainties, stable isotope analyses of carbon, nitrogen, and oxygen have become valuable for reconstructing early hominin habitats and the dietary resources they provided. Carbon and nitrogen stable isotope ratio analyses are routine in assessing animal diets (Sandberg et al. 2012), an approach that relies on the fundamental concept that stable isotope ratios in animals

exhibit direct correlation with the stable isotope ratios found in their diet (DeNiro and Epstein 1978, 1981), which in the case of primates is largely plant based.

For the early fossil record, carbon stable isotope ratios are emphasized because nitrogen is lost during the fossilization process (Shipman et al. 1984). The principal factor contributing to variations in carbon stable isotope values is the specific photosynthetic pathway employed by plants (Smith and Epstein 1971). Most plants use a $C_3$ or $C_4$ photosynthetic pathway, with the terminology denoting the first molecule synthesized upon the uptake and photosynthetic incorporation of atmospheric $CO_2$ (O'Leary 1988). The $C_3$ photosynthetic pathway is ancestral and $C_3$ plants encompass the majority of the world's herbaceous trees and plants, including rice, wheat, soybean, and temperate grasses (O'Leary 1988); $C_4$ plants are arid-adapted and consist predominately of the world's tropical grass species, such as sugarcane, sorghum, and maize, as well as some sedges (Peters and Vogel 2005). Because animals record the stable carbon isotope ratios of their diet in their tissues (DeNiro and Epstein 1978; DeNiro et al. 1985), we know that pure grazers in eastern and southern Africa exhibit $C_4$ signals whereas browsing fauna and nonhuman primates exhibit predominantly $C_3$ signals (Schoeninger 2014). Several variables other than the photosynthetic pathway affect the final carbon isotope composition of a plant (or the $\delta^{13}C_{plant}$ value; Marshall et al. 2007), and $C_3$ plants are affected to a far greater extent than $C_4$ plants are (Marino and McElroy 1991). Specific $\delta^{13}C_{plant}$ values result from a balance between the photosynthetic rate and the $\delta^{13}C$ value of the $CO_2$ available to the plant, both of which are impacted by available water, altitude, temperature, plant phylogeny, canopy cover, and leaf type (Farquhar et al. 1989). Animals feeding on $C_3$ plants, such as nonhuman primates, will record their local ecology in their tissue $\delta^{13}C$ values including the photosynthetic pathway of the plants on which they feed, or that of the plant foods of their animal prey.

Decades of stable isotope research on $C_3$, $C_4$, and composite diets among Plio-Pleistocene hominins reveal a complex picture of resource use. Some pre-*Homo* species—such as *Ardipithecus ramidus* and *Australopithecus anamensis*—relied heavily on $C_3$ plants from woodlands and forests (White et al. 2009a,b; Henry et al. 2012; Quinn 2019). Others—such as *Australopithecus africanus*, *Australopithecus afarensis*, and *Australopithecus bahrelghazali*—consumed significant amounts of $C_4$ grasses and sedges from open tropical savannas (Lee-Thorp et al. 2012; Wynn et al. 2013; Sponheimer et al. 2023; Teaford et al. 2023). Stable isotope approaches have also been applied to later hominins. Nitrogen values in Neanderthals, long interpreted as evidence of a heavily meat-based diet (Richards et al. 2000; Soficaru et al. 2006; Bocherens 2009; El Zaatari et al. 2011), illustrate the pitfalls of straightforward isotope–diet linkages. Recent work shows that high nitrogen isotope signatures can result from consuming invertebrates such as maggots feasting on animal tissues, which can be extremely enriched in nitrogen (Beasley et al. 2025). Such findings emphasize that isotopic enrichment does not necessarily imply a diet dominated by fresh red meat, but could equally reflect nutrient-rich tissues from decomposing animal remains—where the maggots and their decaying food source are a nearly inseparable package deal. Complementary evidence from dental calculus and phytolith recovery propose that Neanderthal diets also included several wild plant foods such as barley and tubers (Henry et al. 2011).

Evidence of early hominin diet composition also comes from dental microwear analysis, which examines patterns of scratches and pits on tooth enamel that reflect prior dietary history. Species that shear their food (e.g., leaf and muscle-meat eaters) tend to exhibit more long parallel scratches, whereas hard-object feeders (e.g., consumers of nuts and bones) tend to have more pitted enamel surfaces (Teaford et al. 2023). Such analyses have been applied to early hominins, with microwear textures in *Australopithecus* species suggesting diets not dominated by hard foods, since their enamel generally lacks the heavy pitting anticipated from their dental morphology (Ungar and Sponheimer 2011). This has been interpreted as evidence that meat/bones and/or tough leaves were

not routine dietary staples. Others have posited that *Australopithecus* may have processed fibrous foods between their teeth in a grinding motion, akin to using a mortar and pestle (Ungar et al. 2010). The South African "robust" australopithecines do, however, show hard-object wear patterns characterized as a "fall back" strategy, in which harder items were consumed when softer foods were unavailable (Scott et al. 2005). Early members of the genus *Homo* display microwear patterns consistent with a more generalized diet, dominated by neither hard nor tough-to-chew foods (Ungar and Sponheimer 2011). For an expanded discussion, see Plummer et al. (2023) and Thompson et al. (2019), which review the use of Oldowan tools in animal butchery and the origins of early hominin exploitation of large-animal resources, respectively.

By the early Pleistocene, multiple lines of evidence ranging from butchery marks to isotopic data indicate that hominins incorporated animal-derived foods into their diets (Domínguez-Rodrigo et al. 2021), alongside other plant and invertebrate resources, reflecting considerable dietary breadth within species (Fiorenza et al. 2015; Beasley et al. 2025). Importantly, such breadth did not necessarily place them in direct ecological competition with large carnivores, in part because modern humans and other carnivores differ markedly in nutritional requirements. Although it stands to reason that early hominins should have engaged in direct and possibly deadly competition with other carnivores, this does not seem to be the case, given the rarity of large-carnivore damage on hominin remains (Hart and Sussman 2011; Saladié et al. 2014; Daujeard et al. 2016; Camarós et al. 2017). These observations raise the possibility of occasional mutual tolerance at carcass sites, with the "value" of the animal remains determined less by its protein content than by whether it met the forager's specific energetic and physiological needs—such as humans' limited ability to derive energy from protein and their greater reliance on fat- and carbohydrate-rich foods.

Speth (2024) argues that interactions between humans and carnivores in the past may have been considerably less confrontational and less centered on acquiring protein, with greater emphasis on securing fat, oils, or carbohydrate-rich resources regardless of their source (Speth 2024). Instead, these interactions may have involved a form of guarded mutual tolerance, facilitation, and occasional mutualism, particularly in scenarios where both parties had access to sufficient animal carcasses. This hypothesis takes into consideration widespread observations and fundamental distinctions in nutrition and metabolism between humans, who descended from predominantly vegetarian primates, and hypercarnivores (e.g., hyenas, felids, African hunting dogs, and wolves) that are highly specialized meat-eaters with a significantly higher tolerance for protein. The substantial quantities of lean muscle tissue present on most large ungulates, such as the thighs and shoulders, offer greater nutritional value to hypercarnivores (Van Valkenburgh 1988; Holliday 2010) than they do to humans, since such predators are well adapted to high-protein meals, while humans are not. In hypercarnivores, proteins can comprise up to 50–70% of their caloric intake (Van Valkenburgh 1996; Eisert 2011; Hewson-Hughes et al. 2013; Schermerhorn 2013; Kohl et al. 2015). Consequently, hypercarnivores fare better with much lower fat intakes, thereby introducing the possibility of mutually beneficial interactions dealing in an exchange of lean meat for fatty tissue (Bronstein 2015; Speth 2024). Early hominins, scavenging primarily for fatty mammalian tissues and armed with sharp flakes and heavy chopping tools, could access nearly any part of large animal carcasses, potentially creating advantageous opportunities for other meat-eating species if protein-rich muscle tissue were left behind.

Hunter-gatherer societies worldwide have a strong preference for fatty tissues over mammalian muscle meat, where the most desired animal parts include subcutaneous fat deposits, fatty tissues from the brain, marrow, and the fat padding of internal organs and intestines (Speth 2022a,b). In contrast, wild ungulate muscle meat—irrespective of season, sex, or reproductive state—contains minimal lipids (Speth 2022a). From a caloric standpoint, this is significant because hunter-gatherers cannot safely exceed roughly 250–300 g of

protein per day without risking "rabbit starvation," described earlier (Speth 2025). The only "cure" is replacing some protein-rich foods with fat- or carbohydrate-rich sources (Speth and Spielmann 1983; Speth 1987), a tradeoff that seems to have shaped the fundamental dietary strategies among hunter-gatherers (Speth and Spielmann 1983; Speth 1987, 1989, 2010, 2022a), especially in mid- to northern latitudes (Speth 2025). Because humans are physiologically constrained in the amount of protein they can safely consume, the remaining caloric needs must be met by these nonprotein sources. In an examination of 167 faunal assemblages across 63 Western European Paleolithic and early Holocene sites, marrow utility—rather than muscle meat or overall food utility—emerged as the most reliable predictor of bone transportation, showcasing its value as a portable, energy-dense resource (Morin and Ready 2013). Nevertheless, interpreting preferences such as these in the archeological record is fraught with challenges. To reiterate, while "filleting" notches on long bones (e.g., such as the femur and humerus) are often used as evidence of muscle meat's evolutionary significance, these cut marks could alternatively represent the removal of lean muscle to access fat-rich marrow beneath.

To summarize, the lineage leading to modern humans undoubtedly relied on a diet that included increasing amounts of animal foods. Our ancestors appear to have been adaptable omnivores whose foraging strategies balanced fat acquisition with carbohydrate-rich plant foods to avoid the metabolic shortfalls of excessive protein intake. Obtaining animal foods, especially from large prey, likely required increased cooperation and planning as well as more complex technology, ranging from extractive tools to hunting weapons and fire use. Within this framework, red meat could indeed have been a "blessing."

## Consumption of Meat During the Transition to Agriculture to the Present

Hunters in the late-Paleolithic and Mesolithic periods in boreal and subboreal environments ate a diet composed of both plant and animal resources, with much of the dietary protein coming from animal meat (Richards 2002), especially during the winter months. Notwithstanding the method by which our hominin ancestors obtained nutrient-dense animal foods—whether through hunting or scavenging or through heightened competition with large carnivores (Brantingham 1998; Hart and Sussman 2011, 2018; Stiner 2012; Geist 2014, 2016; Daujeard et al. 2016; Rodríguez-Gómez et al. 2017) or coexisting with mutual tolerance, once early hominins began regularly integrating other vertebrates into their foraging routines, the practice became universal.

The transition from hunter-gatherer to agricultural societies, approximately 12,000 to 10,000 years ago with the cultivation of plants and the domestication of animals, allowed for more reliable access to food year-round and supported rising population densities. Termed the *agrarian revolution*, this transformation was spurred by a combination of factors, including a warming climate, stronger seasonal fluctuations, and the disappearance of larger animals due to events such as the great megafauna extinction (Stuart 2015; Matranga 2024), the loss of numerous large-bodied species from various ecosystems across the globe (Figure 2). These events profoundly altered ecological dynamics, leading to shifts in food availability and resource distribution, which have long been argued to be a motivating factor for early humans to adopt agricultural practices. The agrarian revolution stands as a crucial juncture in the evolution of human culture, reshaping societal structures, patterns of living, and several aspects of human biology.

The shift to agricultural societies meant that food, like red meat, became more easily accessible and could even exist in surplus (Smith 1995; Diamond 1999; Larsen 2003). The cultivation of cereals (including rice, maize, wheat, barley, millet, and sorghum), pulses, and tubers led to a significant increase in the caloric yield per unit of land. However, the preference for the consumption of one or two cultivated crops led to a reduction in the diversity of food sources and in the nutritional status among agrarian

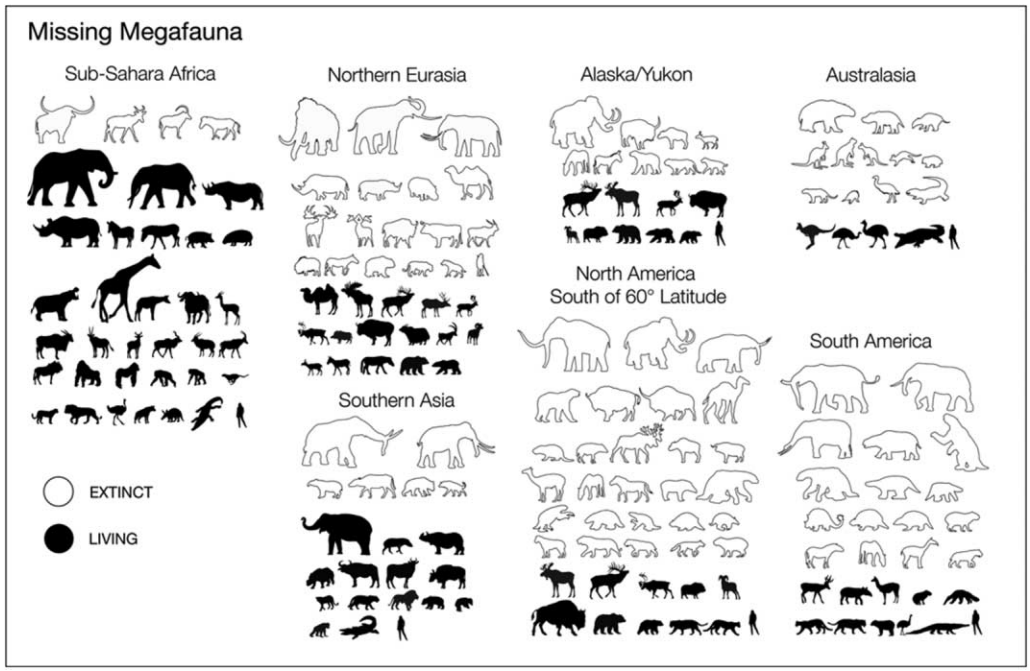


FIGURE 2. MISSING MEGAFAUNA

Living and extinct megafauna across all continents in the Late Quaternary. While Sub-Saharan Africa retained most of its fauna, extinction severity varied greatly among zoogeographical regions, with North America, South America, and Australia experiencing the greatest losses. These extinction events largely predated the agricultural revolution. It has been suggested that wherever humans arrived and population densities increased, direct competition and intensified hunting pressure ensued. However, the causes of Late Quaternary megafaunal extinctions remain debated; leading hypotheses include animal overkill, environmental shifts, and/or their interaction. Figure drawn based on data from Stuart (2015); see also Svenning et al. (2024). Compared with Stuart (2015), this rendering adds both species of *Gorilla* and both species of *Pan*, as well as cheetahs and gerenuks in Africa and *Rhea* birds in South America.

populations (Larsen 1995; Diamond 1999), a trend that has continued to this day as a mere four crops (maize, rice, soybean, and wheat) provide one-half of the world's food calories even though more than two million distinct crop varieties are recorded in seed vaults (Allender 2011). Despite reductions in food diversity, caloric intake increased, and human populations experienced accelerated growth rates, attributed in part to an elevated number of children and pregnancies per family, which themselves are influenced by a shortened duration of breastfeeding, leading to much shortened interbirth intervals. Expanding populations, in turn, fueled more farming as agriculture can provide more food than foraging, resulting in a positive feedback loop between population growth and increased food production. The quantity of meat from domesticated animals such as sheep, goats, pigs, cows, and poultry (in that order) lagged behind the expanding human populations (Larsen 2003) and, consequently, the relative intake of meat actually *decreased* in these settled populations, accompanied by increased consumption of cereal grains, pulses, and tubers. Moreover, many societies in Europe, Asia, and Africa augmented their diets by exploiting milk from their domesticated animals (Stock and Wells 2023).

By the late 19th century, however, more transformations were underway, propelled by the advent of the Industrial Revolution and global human population reached one billion. Foremost among these changes were

the fast-paced processes of urbanization and industrialization that reshaped numerous facets of society. These included notable changes in food production, processing, and distribution. Improved transportation systems and refrigeration facilitated distribution to urban areas and beyond, extending the reach of various canned and processed food products, many of which experienced widespread availability for the first time. In other words, food became more readily available again. Massive declines in infant mortality came about through the spread of improved sanitation including tap water chlorination and pasteurization in the early 20th century (Bhatia et al. 2019).

Rising household incomes also fueled these fundamental shifts in dietary preferences and lifestyle patterns (Smil 2013), and higher meat intake became an integral part of this transformation, initially taking hold in Europe, North America, Australia, and Japan. Most animal feed also benefited from much higher crop yields achieved via the combination of synthetic nitrogen fertilizer (thanks to the energetically costly Haber-Bosch method of nitrogen fixation) and selective crop breeding, which ushered in the green revolution.

By the latter half of the 20th century and the early 21st century, these trends accelerated worldwide, increasing severalfold in rapidly growing economies and densely populated countries in South America and Asia. Between 1998 and 2018, global meat consumption rose by 58%, with low-income countries accounting for approximately 85% of this expansion, which was predominantly driven by population growth (accounting for 54% of the overall increase) and increased production (Whitnall and Pitts 2019). The rise in per capita consumption of meat became strongly influenced by changing consumer preferences and income growth. Across the world there is much variation in attitudes toward meat eating between subgroups as explained partly by age, sex, ethnicity, and income differences (Pfeiler and Egloff 2018; Zeng et al. 2019). Cultural traditions, religious taboos, and economic realities also intrinsically dictate the type and degree of consumption.

As an example, India, the most populous nation on Earth, illustrates the challenges in defining whether a country is a "high red meat consumer." Although India maintains a relatively high consumption of bovine (cow and water buffalo) milk, especially compared to more lactose-intolerant regions such as Southeast Asia and parts of Africa, India also has the world's second largest Muslim population—and most Indian Muslims consume red meat (other than pork). Consequently, meat intake has continued to exhibit a consistent and culturally dynamic pattern over time, where variations in both the quantity and types of red meat consumed vary globally (notably, vegetarian foodways only became possible after the adoption of farming and with the development of cereal and pulse domestication, as there are no preagricultural vegetarian societies on record). Although nuances within countries are the rule, one thing remains certain: over the last 50 years, there has been a rapid increase in meat production across the globe (Ritchie et al. 2017).

Current meat consumption is higher than ever in modern history, a trend that has only partially reversed over the last few years in some affluent countries (Stewart et al. 2021; Lehto et al. 2022), but is completely offset by the swelling demand for meat in low-income countries (Speedy 2003; Walker et al. 2005; Whitnall and Pitts 2019). The global per capita consumption of meat is driven by a diverse set of factors, namely population growth, rising incomes, and widespread sociocultural traditions prioritizing daily meat consumption and its associated prestige—a symbol of wealth, power, and status (Zaraska 2016; Godfray et al. 2018; Milford et al. 2019). The United States continues to rank among the highest per capita beef consumers globally, second only to Argentina (Organisation for Economic Co-Operation and Development 2023), despite prior guidelines recommending reduced red meat consumption (Willett et al. 2019) that, at this point, are based on several decades of observations demonstrating lower rates of chronic disease in populations that either abstain from red meat entirely or consume it at very low levels (Fraser 1999; Key

et al. 1999; Singh et al. 2003; Bleich et al. 2026; Giosuè et al. 2026).

Notwithstanding a growing interest in leaner cuts and some increase in white meat intake among health-conscious consumers in high-income countries (Neff et al. 2018), red meat still constitutes a major proportion of all meat consumed in the United States, with nearly a one-quarter coming from processed forms (for example, hot dogs, bacon, sausages, and deli meats; Daniel et al. 2011). The increasing demand and the globalization of many economies has led to a decline of traditional practices and an increase in the industrialization of livestock rearing, feeding, transport, and slaughter. Adult cattle are, on average, over 30% heavier today than they were just three decades ago (McMurry 2008), requiring 22% more daily maintenance energy (National Research Council 2001). Selection for rapid growth and large mass, among other practices (including antibiotic feeding to fatten herds), have contributed to substantial increases in mature cow weight ( Jenkins and Ferrell 2006) that, unsurprisingly, necessitate far greater daily intake of feed compared to smaller cows (Walker et al. 2015). Average time to reach adult weight for a pig raised with modern feeding practices—and safeguarded by antibiotics, which also promote weight gain—is now about 24 weeks, compared to roughly two to three years for wild pigs to reach full maturity; time from birth to slaughter is also significantly reduced for calves (Smil 2013). Hence, the life cycles, body mass, and nutrient composition of livestock are fundamentally altered compared to what early humans likely experienced preagriculture. Taken together, the gradual adoption of dietary patterns emphasizing greater quantities of meat often supplants the inclusion of whole grains and other plant-based foods (Krebs-Smith 1998; Terry et al. 2001) inherent to many ancestral diets.

It is worth mentioning that meat consumption likely shaped many "inherent" human characteristics, both as a physical and conceptual resource, long before humans ever transitioned to agricultural societies. This extends to varied factors such as cooperation and reciprocity, societal differentiation and hierarchical positioning, gender distinctions, power dynamics, religious beliefs and practices, cultural expression, and personal identity (Leroy and Praet 2015). Although beyond the scope of this review, the significance of meat—including its roles in sharing systems, social status, and ritual practices such as animal sacrifice—is abundantly evident, having been well documented across diverse societies. Leroy and Praet (2015) offer an expanded perspective on meat consumption during human evolution, exploring the cultural predispositions and prescriptions that are bound to influence future trends in red meat consumption.

## Meat Consumption Among Current-Day Hunters and Gatherers

The diets of contemporary hunting and gathering (foraging) populations are used as a reference standard for the evolution of human diet and are habitually thought of as representative of the "true" Paleolithic diet (Eaton and Konner 1985; Cordain et al. 2002). Although hunter-gatherer communities today are not direct replicas of Paleolithic populations, their mobile lifestyles and subsistence strategies—features that have characterized over 95% of human prehistory—make them among the best available models for understanding the significance of meat in foraged diets.

Despite several attempts to characterize a universal hunter-gatherer diet, no generalized dietary pattern exists beyond the general observation of more meat being eaten in the far north compared with the equatorial regions, due to wide variation in ecology, climate, seasonality, and available resources across communities (Eaton 2006; Ströhle and Hahn 2011; Kelly 2013; Crittenden and Schnorr 2017). Based on the energetic contribution of foods, mean subsistence economies have been estimated for over 200 foraging populations to date. The results of one review (Cordain et al. 2000) concluded that most foraging populations obtain approximately one-half of their diet's calories from animal foods, but this finding is controversial because the accuracy of the data is highly variable. In tundra environments with limited

foliage, for example, meat contributes up to 86% of the diet; in grassland ecosystems, the value drops to between 42–62% of the diet; and in forests (temperate and rainforests) meat may make up 52–80% of the total diet (Cordain et al. 2000). More recent quantitative nutritional and ecological data reveal that among subtropical foragers, meat comprises only approximately 40% of the diet (Berbesque et al. 2011; Kelly 2013; Crittenden and Schnorr 2017). Among foragers, animal consumption extends beyond muscle tissue to include virtually all edible parts of the carcass—organs, bone marrow, brain and, occasionally, the fermented contents of its upper GI tract (Buck et al. 2016). Moreover, many of these populations additionally consume some quantity of insects, which would be listed as animal products in the ethnographic record and in nutritional tabulations (Lesnik 2014; Marlowe et al. 2014; McGrew 2014). Insights from all of these data do not support the notion of a *single* evolved diet but point to red meat as a significant part in all of these diets.

What is certain is that in ecosystems where it is available, all types of available wild game likely had important, albeit variable, roles in preventing undernutrition for foraging people, as it not only provided a source of protein and fat, but vitamins A, B1 (thiamin), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B12 (cobalamin), C (ascorbic acid), iron, phosphorous, zinc, and selenium. Organ meats (e.g., liver, kidney, brain, heart, and tripe) demonstrate a robust assortment of these life-supporting macro- and micronutrients (Beal and Ortenzi 2022). Although the consumption of these organ meats is not nearly as high as muscle meat worldwide (but certainly more frequent in present-day hunter-gatherers), its importance in the Paleolithic period is relatively unknown. Deficiencies in any of these individual nutrients can cause debilitating or even fatal diseases depending on the life stage of the individual. Thus, many vertebrates likely served as essential nutritional resources during developmental periods or in times when more reliable or accessible plant-based foods were scarce, although their precise relative importance remains largely unspecified.

## Meat's Broader Nutrient Contributions: Proteins, Fats, and Beyond

Despite variation across species, breeds, feeding regimens, seasons, and meat cuts (Bunn and Ezzo 1993), skeletal muscle meat is nutritionally valuable. It provides essential amino acids, B complex vitamins, micronutrients, and minerals such as heme iron—which imparts its red color—but it is generally less energy-dense than fat-rich organs (Higgs 2000; Beal and Ortenzi 2022). Beyond these well-known nutrients, meat delivers a suite of often-overlooked but physiologically important compounds, including creatine (De Guingand et al. 2019; Ostojic and Forbes 2022), L-carnitine (Belay et al. 2006; Ferreira and McKenna 2017), and choline (Zeisel and da Costa 2009; Wiedeman et al. 2018). Creatine and L-carnitine are conditionally essential, meaning that under certain physiological states—such as rapid growth, pregnancy, or in neonates—endogenous synthesis may be insufficient to meet metabolic demands. Choline, by contrast, is essential, as endogenous synthesis alone cannot satisfy human requirements, especially under high-demand physiological states, and needs to be consumed in the diet for optimal growth and development. These compounds collectively underpin energy metabolism, mitochondrial function, and methylation pathways, respectively. Variations in dietary intake or endogenous synthesis of any one of these nutrients may have direct implications for growth, especially during fetal development (De Guingand et al. 2019; Manninen et al. 2022; Derbyshire 2025).

Raw red muscle meat contains approximately 20–25 g of protein per 100 g, whereas cooked red muscle meat contains approximately 28–36 g per 100 g of protein due to drip loss and water evaporation (Williams 2007). With optimal digestive function (e.g., sufficient stomach acid, digestive enzymes, and absorptive function), mammalian meats are highly digestible when cooked, at 94% compared to 86% in whole wheat and 78% in beans, making it a premier source of digestible protein (Williams 2007). Red meat contains adequate shares of all of the essential

amino acids (lysine, threonine, methionine, phenylalanine, tryptophan, leucine, isoleucine, and valine), in addition to the conditionally essential amino acid taurine—a large component of the free amino acid reservoir in mammalian blood and tissues (Sturman et al. 1977; Sturman 1981). Unique in that it does not form peptide bonds with other amino acids, taurine (derived from the Latin word for bull) is a sulfur-containing organic acid mainly synthesized in the liver. Although several biosynthetic pathways exist in animals, for brevity, we focus here on the primary route involving cysteine: first converted to cysteine sulfinic acid by the enzyme cysteine dioxygenase, then decarboxylated by cysteine sulfinic acid decarboxylase (CSAD) to form hypotaurine, which is subsequently oxidized to taurine (Huxtable 1992). Fetuses and infants have limited capacity for endogenous taurine production due to lower activity of enzymes such as CSAD and cystathionine γ-lyase in their nascent livers and brains (Sturman and Hayes 1980). For that reason, fetuses and infants rely heavily on the taurine provided by their mothers through the placenta or breast milk (Lambert et al. 2015; Tochitani 2017), which perhaps explains why taurine is the second most abundant free amino acid in human breast milk, after glutamate (Sturman et al. 1977).

Red meat contains several types of fat, each with distinct properties. Triglycerides are the most abundant and consist of glycerol molecules bonded to saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), or polyunsaturated fatty acids (PUFAs). Trans fatty acids (TFAs) are present in much smaller amounts, making them rarer than SFAs, MUFAs, and PUFAs. Cholesterol, a lipid found throughout animal tissues, is also present, contributing to the formation of cell membranes and certain hormones.

Triglycerides in red meat provide two essential fatty acids: linoleic acid (an omega-6 PUFA) and alpha-linolenic acid (an omega-3 PUFA), which are necessary for synthesizing many critical regulators. Red meat also contains other omega-3 PUFAs, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are critically important during pregnancy and lactation and are associated with a reduced risk of several chronic diseases (Pereira and Vicente 2013). Marine animal foods provide the greatest dietary sources of these omega-3 PUFAs.

Red meat contains trace amounts of naturally occurring TFAs, which are produced by biohydrogenation in the rumen, where bacteria convert unsaturated fatty acids into molecules containing one or more double bonds in the *trans* configuration. Although some naturally occurring TFAs have been suggested to possess potential antioxidant properties (Flintoff-Dye and Omaye 2005; Putera et al. 2023), the exact mechanisms by which they positively influence oxidative stress and inflammation have yet to be determined (Nakamura et al. 2008; Putera et al. 2023). Synthetic TFAs, on the other hand, produced via industrial hydrogenation of various plant oils, are largely associated with an increased risk of cardiovascular complications when consumed in excess (Mozaffarian et al. 2006; de Souza et al. 2015).

Contrary to common perceptions, the cholesterol content of red meat is broadly comparable to that of poultry, varying by cut and preparation. As such, both red and white meats can similarly raise low-density lipoprotein cholesterol (LDL-C) in healthy volunteers (Bergeron et al. 2019). Elevated LDL-C levels are frequently found among omnivores (particularly habitual red meat consumers; Bergeron et al. 2019; Hassannejad et al. 2021), compared with vegetarians whose diets emphasize legumes, nuts, grains, and soy products (Key et al. 2006). Still, the mixed outcomes that exist across nutrition studies largely reflect variability in meat quality and processing, accompanying dietary components, and lifestyle factors. For instance, the diet of livestock alters their overall body fat composition: cattle raised on pasture and allowed to roam typically exhibit lower saturated fat and total cholesterol than grain-fed cattle reared in concentrated feeding operations (French et al. 2000; Nogoy et al. 2022). Such differences underscore that the composition of industrially produced meat today diverges markedly from the animal foods consumed by our ancestors.

Finally, all beef, pork, and dairy products lack fiber in the conventional sense. Yet,

red meat contains glycosaminoglycans, such as heparan sulfate and chondroitin sulfate, which could potentially act as substrates for fermentation in the colon. The ability of microbes to utilize complex carbohydrates is, of course, the defining feature of dietary plant-based fibers (Rawat et al. 2022). Energetically, meat provides little carbohydrates for direct energy production; its nutritional value instead comes from the macronutrients, micronutrients, essential, and conditionally essential nutrients discussed above.

Human development is characterized by life stages with particularly high and specific nutritional demands—most notably during pregnancy, lactation, infancy, and prolonged childhood (Sally et al. 2013; Bowman et al. 2021). Pregnancy alone requires a substantial increase in maternal metabolic rate to support both fetal growth and maternal physiological changes, making maternal energetic investment higher in humans than in any other primate. The risks of undernutrition are especially acute during pregnancy and the first two years of life, yet evidence now shows that nutritional status during this window affects not only maternal and infant health, but also the long-term health trajectories of subsequent generations (Kuzawa 2005; Benyshek 2007). While the exact increase in maternal metabolic rate varies with gestational age, body size, and health status, recent estimates suggest it can exceed approximately 2.1 times basal metabolic rate (Cordey et al. 2023). Because of its desirable package of nutrients—including high-quality protein, readily available fats, bioavailable iron, B vitamins, and other micronutrients—mammalian meats have long been argued to help "fill in" critical nutritional gaps during these energetically demanding stages. This perspective helps explain why the availability of animal-derived foods may have constrained fertility, infant survival, and population growth across both hunter-gatherer and early agrarian societies.

## Meat's "Iron" Grip on Human Health: From Evolutionary Necessity to Modern Mismatch?

Of all of the nutrients mentioned above, iron is the most commonly deficient micronutrient across all age groups (Han et al. 2022), even though it is the fourth most abundant element on Earth. Iron deficiency, whether with or without iron deficiency anemia, is so prevalent that it affects people in all regions of the world. In fact, the most significant contributors to the global burden of micronutrient deficiencies are iron deficiency and iron deficiency-related anemia (Patton et al. 2009; GBD 2021 Anaemia Collaborators 2023). For this reason, there has been a long-standing belief that red meat served as a significant source of iron in the human diet.

Iron, as a trace mineral, is required for numerous cellular functions, including DNA synthesis, nucleic acid repair, cell growth and programed cell death, gas transport, cellular respiration in the mitochondria, and cell signaling and host defense (Dev and Babitt 2017; Sukhbaatar and Weichhart 2018). Iron is one of the most indispensable metals needed to sustain life—from single-cell bacteria to the multicellular *Homo* (Silva and Faustino 2015; Schwartz et al. 2019). Adult human bodies contain about 3–4 g of iron (roughly the weight of a 2-inch nail), most of which is found in the form of hemoglobin and myoglobin, heme proteins that exhibit their physiological significance by binding molecular oxygen and $CO_2$ (Johnson-Wimbley and Graham 2011). Absorption, transport, delivery, and storage of iron are elaborate and highly regulated processes that involve numerous cofactors, transport molecules, scavengers, and receptors—many of which are reviewed in detail elsewhere (Conrad and Umbreit 1993; Byrnes et al. 2002; Anderson et al. 2009; De Domenico et al. 2009; Zhang and Enns 2009; Silva and Faustino 2015; Dev and Babitt 2017; Schwartz et al. 2019; Vogt et al. 2021; Ni et al. 2022).

There are no known physiologic mechanisms for selective iron excretion. Systemic iron is efficiently conserved and recycled throughout life. Minimal basal iron losses occur daily through the shedding of cells from the skin, intestines, urinary tract, and airways so, in adult males, dietary iron needs primarily compensate for these basal losses and support cellular growth and maintenance. In contrast, women of reproductive age experience far greater iron loss through menstruation, an

important risk factor for iron deficiency. Menstrual bleeding, the external manifestation of the menstrual cycle's luteal-to-follicular phase transition, usually occurs over three to six days, with the heaviest flow on day two (Mihm et al. 2011). Average blood loss during menstruation is approximately 30 to 40 mL (ranging from 10–84 mL; Mihm et al. 2011), with normal bleeding defined as 5–80 mL per cycle, and light bleeding as less than 5 mL (Fraser et al. 2007). Heavy menstrual bleeding is clinically defined as blood loss exceeding 80 mL per cycle (Hallberg and Nilsson 1964; Fraser et al. 2007). Notably, menstrual blood loss varies with age—women over 50 tend to lose about 6 mL more than younger women—and is influenced by regional and socioeconomic factors affecting cycle length and bleeding duration (Harlow et al. 2013). Given that menstrual blood loss can approach or exceed 80 mL per cycle, iron loss during menstruation may be substantial for many women of reproductive age. In the United States, the required daily iron intakes for a healthy adult male, female, and pregnant female are 8 mg/day, 18 mg/day, and 27 mg/day, respectively, demonstrating stark differences between sexes and the dramatic demands for iron during pregnancy (Trumbo et al. 2001).

In pregnancy, iron requirements rise sharply. This is why GI tract absorption of iron increases severalfold during pregnancy (Hallberg 1988). The placenta retains around 90 mg of iron for its own functions and redirects 270 mg of iron to the fetus during the second and third trimesters (McArdle et al. 2011; Cao and Fleming 2016), possibly explaining why most mammals consume their own afterbirth (Mota-Rojas et al. 2020), with humans and some marine mammals being notable exceptions for unexplained reasons. Newborn infants possess enough iron stores from their mother to last for 4–6 months, after which breast milk alone is insufficient to supply iron. During the latter third of pregnancy, or in the weaning period from 4–6 months to 2 years of age—although it should be noted that in hunting and gathering populations, weaning typically occurs much later (Konner and Worthman 1980; McDade and Worthman 1998; Sellen 2001; McKerracher et al. 2020)—rates of iron deficiency can be quite high and extend into adolescence for both sexes (Patton et al. 2009; Joo et al. 2016). Although extensive recycling of iron allows for a relatively low daily requirement of only 1–2 mg of absorbed iron to counterbalance the iron losses resulting from the shedding of cells (Fleming and Ponka 2012), iron stores have been found to be at their lowest levels in menstruating women (Chandra et al. 2017), with estimates suggesting 1–2 mg of iron loss daily (Steinbicker and Muckenthaler 2013). The evolutionary origins and consequences of menstruation in human females, including the factors contributing to the monthly and nontrivial blood loss, still lack satisfactory explanations, as does ubiquitous iron deficiency as we define it. Across mammals, however, there appears to be a strong correlation between more blood loss during menstruation and the presence of invasive forms of placentation and the derived process of spontaneous decidualization (i.e., the proliferation of the endometrium without a signal from the fetus; Emera et al. 2012). Comparatively, great apes seem to experience less blood loss during menstruation when compared with humans (Dixson 2012). One potential rationale behind the increased blood loss in humans could be linked to the divergent timing of the birthing process, where placental detachment is governed by a similar mechanism involving the abrupt withdrawal of progesterone (Thomas 2019). We must, however, take caution over interpretation of menstrual blood loss, as we lack data on small-scale, nonindustrial populations who have limited access to biomedical birth control and where women experience far fewer lifetime menstrual cycles because of increased number of pregnancies, extended breastfeeding, and lactation-induced amenorrhea.

The prevalence of iron deficiency is explained largely by its poor bioavailability in certain food groups. Dietary iron exists in two forms, heme and nonheme bound iron (Abbaspour et al. 2014). Most iron in the diet, accounting for over 88% on average (Raper et al. 1984), exists as nonheme iron and is primarily composed of iron salts. Whereas nonheme iron is present in whole-grain cereals,

legumes, nuts, seeds, and certain vegetables, heme iron occurs in the hemoglobin and myoglobin of red meat and, to a lesser extent, poultry and fish (Abbaspour et al. 2014). Although heme iron contributes only approximately 10–15% of total dietary iron intake in meat-eating populations, it accounts for more than 40% of total absorbed iron (Carpenter and Mahoney 1992; Hunt 2002). Notably, heme iron also enhances the absorption of nonheme iron through a mechanism that remains incompletely understood (Piskin et al. 2022). Importantly, the significance of nonheme iron sources should not be dismissed on the basis of their lower iron content or reduced bioavailability. The absorption of nonheme iron depends heavily on its solubility in the proximal small intestine, which is strongly influenced by the overall composition of the meal (Hallberg 1981; Charlton and Bothwell 1983). On its own, nonheme iron is poorly absorbed, has lower bioavailability than heme iron, and its uptake can be significantly inhibited by substances such as phytates (in cereals), tannins (in tea), and other polyphenols in many vegetables, black tea, and coffee (Charlton and Bothwell 1983; Cook 1990). All of these substances decrease the intestinal solubility of nonheme iron from the entire meal, thereby inhibiting iron absorption. Foods high in ascorbic acid, however, substantially enhance the absorption of iron from the meal by maintaining the solubility of nonheme iron. Compared to water, orange juice approximately doubles the absorption of nonheme iron from a meal; tea and coffee, conversely, decrease the absorption of nonheme iron by over 50% when compared to water (Rossander et al. 1979; Hallberg 1981). Therefore, it is possible that a dietary transition enhancing iron absorption became more favorable over time. Incorporating meals that included iron absorption enhancers such as the combination of meat and fruits/vegetables rich in ascorbic acid—while concomitantly tapering the consumption (or altering the timing) of strong inhibitors—became a serendipitous way to prevent iron deficiency during critical and costly developmental windows (Monsen et al. 1978).

The source of iron and, more importantly, meal compositions may have had major implications in mitigating iron deficiency throughout human evolution. It is unlikely that any agrarian society achieved perfectly balanced diets. In fact, a rise in the frequency and severity of iron deficiency was a significant consequence of the dietary transition during the agrarian revolution (Larsen 1995). The high phytate content in cereals diminished the availability of iron from other foods, and together with a less varied diet—one that lacked enhancers of iron absorption (e.g., ascorbic acid-containing fruits and vegetables)—the challenges of nonheme iron absorption were only exacerbated. Despite the increased consumption of dairy products in certain populations, first made available through the domestication of sheep, goats, cows, buffalo, and camels, iron absorption did not experience a corresponding rise because mammalian milk constitutes both a poor source of iron and a rich source of strong iron chelators, including mammalian lactoferrin (Cook 1990). Lactoferrin is a potent iron-binding glycoprotein that forms an essential component of many body processes such as mucosal innate defenses (Ahmed et al. 2021). Sometimes, the introduction of cow's milk, given to infants, has triggered intestinal bleeding, further contributing to iron deficiency anemia (Ziegler et al. 1999; Jiang et al. 2000). Moreover, the use of eggs—widely available after the domestication of chickens, ducks, and geese—likely resulted in further reductions in nonheme iron absorption (Cook 1990; Weinberg 1993). Egg yolk contains iron-binding proteins such as phosvitin, while egg white contains ovotransferrin, both of which can sequester iron and limit its bioavailability (Albright et al. 1984; Sato et al. 1987; Baron et al. 1997; Kang et al. 2006). All in all, the dietary transition of the agrarian revolution had lasting negative biological impacts, some of which are detectable in skeletal remains. Archeological evidence suggests that advanced iron deficiency anemia was more common in agricultural populations than in their hunter-gatherer counterparts, often indicated by more porous or spongy bones (e.g., cribra orbitalia and porotic hyperostosis) and a higher

prevalence of periodontal diseases (Larsen 1995, 2003).

Modest iron deficiency may also represent evolutionary tradeoffs, offering advantages in certain environmental contexts and disadvantages in others (Wander et al. 2009). Hemochromatosis, an inherited disorder characterized by systemic iron overload and eventual iron-induced toxicity to various organs represents the opposite side of the spectrum. Hemochromatosis results from an inability to regulate dietary iron absorption and release iron from aging red blood cells (Adams et al. 2023). Several genes associated with hemochromatosis (*HFE*, *HJV*, *HAMP*, *TFR2*, *FNP1/SLC40A1*, and *PIGA*) enhance iron absorption and should, in principle, act as a safeguard against iron deficiency in vulnerable populations, particularly women of childbearing age. Carriers (heterozygotes) of mutations at these genes typically exhibit normal or marginally increased iron stores with a variable tendency toward hyperferremia (excess blood iron) but often experience no adverse health outcomes, especially in premenopausal females. Yet, apart from the *C282Y* and *H63D* mutations in the human homeostatic iron regulator protein (*HFE*) gene, which enhance iron absorption in the small intestine (Pietrangelo 2004), the global frequency of these mutations is very low in non-European populations, with prevalences of *C28Y* and *H36D* being less than 1% and 4%, respectively (Le Gac and Férec 2005). The explanation for the limited prevalence of common hemochromatosis mutations is puzzling given the biological basis of iron in the body and the many challenges of obtaining sufficient stores from the surrounding environment. Even a true hemochromatosis diagnosis (e.g., homozygosity of *C282Y* mutations in *HFE*) rarely progresses to clinical hemochromatosis or causes death (Beutler et al. 2003; Schmitt et al. 2005; Allen et al. 2008), although increased morbidity in both men and women is now appreciated (Atkins et al. 2020), emphasizing timely diagnosis and initiation of iron reduction therapy. Nonetheless, it is conspicuous that, in the absence of cirrhosis, there appears to be no difference in long-term survival (up to 25 years of follow-up) between untreated individuals with homozygous *C282Y* genotypes and those lacking *HFE* mutations (Andersen et al. 2004; Adams 2009). Individuals homozygous for *C282Y* have only a slightly higher rate of mortality than those without *HFE* mutations (Atkins et al. 2020; Adams et al. 2021), but generally exhibit excellent prognosis. In other words, the impact on the frequency of *C282Y* in these populations, stemming from a balanced polymorphism, appears to be minimal, an observation that supports the finding of similar allele frequencies in both younger and older generations within the same population (Beutler et al. 2003; Schmitt et al. 2005). The same reasoning holds true for the *H63D* allele, which exhibits a milder phenotype compared to the *C282Y* allele (Beutler et al. 2002; Adams et al. 2005; Pilling et al. 2019). Of course, left untreated, the iron-mediated toxicity of hemochromatosis in males (and postmenopausal females) can become life-threatening, resulting in injury to the liver, heart, brain, pancreas, and bones. Although the progression of organ damage in individuals with the genetic condition is closely associated with the extent of iron accumulation at the time of diagnosis (Adams et al. 1997), it is not a strong correlation, suggesting the presence of concurrent factors that either shield against or worsen iron-related injuries (Moirand et al. 1997; Atkins et al. 2020; Adams et al. 2023). Despite this condition's intuitive connection to red meat consumption, the relationship between dietary iron and the development and progression of hemochromatosis is obscure, with insufficient evidence to date to establish official recommendations (Gordeuk et al. 2012). In fact, no specific dietary guidelines are advised since dietary modifications alone are not adequate to substitute for iron depletion through chelating agents or phlebotomy. There may be some obvious protective effects from vegetarian or vegan diets; the latter completely lacks heme iron, yet because no definitive dietary recommendations of iron intake exist, it should challenge what we think we know about dietary iron in nonhemochromatosis populations and in human evolution, as we moved from hunter-gatherer to agricultural societies.

Iron is equally indispensable for all microorganisms. When infected, humans tend to reduce the availability of iron by synthesizing

apoferritin, a protein that binds to free iron molecules and sequesters this nutrient source. Accordingly, serum iron level decreases and serum ferritin, a highly conserved intracellular iron-storage protein, increases. Although this immediate, nonimmunologic protective mechanism involving iron likely predates the evolution of immune defense in mammals (Weinberg 1974, 1993, 1999; Weiss 2002), bacteria, fungi, and certain viruses have evolved a plethora of tricks to steal iron from their hosts. *Yersinia* strains and other members of Enterobacteriaceae, including *Escherichia coli*, *Klebsiella*, *Shigella*, and *Salmonella*, produce high-affinity proteins known as siderophores that extract iron from the host's binding proteins and subsequently internalize the iron-siderophore complex—of note, the virulence of *Yersinia* strains is directly linked to the efficiency of their iron-transport systems (Carniel 2001).

The evidence linking iron deficiency to *protection* against bacterial infection (Ell 1985; Harvey et al. 1985; Allen et al. 1997; Carniel 2001; Caza and Kronstad 2013; Chang et al. 2015; Ganz and Nemeth 2015) and iron excess to *susceptibility* of infection abounds (Oppenheimer et al. 1986; Vadillo et al. 1994; Weinberg 2000; Gangaidzo et al. 2001; Lounis et al. 2001; Collins 2003; Nyakeriga et al. 2004; Esan et al. 2013; John 2013; Clark et al. 2014). Epidemics of malaria, tuberculosis, and various other infections were pervasive spanning the past 500+ generations, a time frame that must have provided much opportunity for selection of more resistant iron-deficient phenotypes (Denic and Agarwal 2007). Historical accounts documenting a predominance of men (a demographic subgroup with a lower likelihood of experiencing iron deficiency) as victims during plague epidemics (Chanteau et al. 2000) also fit the pattern. Hereditary hemochromatosis independently reduces the number of circulating and hepatic CD8 cells, natural killer T cells (associated with serum ferritin and transferrin saturation), and the activity of cytotoxic T lymphocytes, in addition to abnormally altering the CD8+ T cell pool and T lymphocyte cell surface molecules (Bahram et al. 1999; Cardoso and De Sousa 2003; Khan et al. 2007). Iron is necessary for robust defenses in immune cell proliferation, but also compromises the entire system when present in excess. Moreover, the first food of infant life, mother's milk, contains lactoferrin, which further acts as an antimicrobial agent because of its ability to strongly bind and sequester iron away from virulent pathogens. Lactoferrin is found in various body fluids and within neutrophil granules (Weinberg 1993). The occurrence of low iron intake/absorption during early childhood aligns with the period of peak mortality from infectious diseases in human life history (Lopez et al. 2006). This indirect correlation supports the idea of protection conferred by relative iron deficiency.

The above data would suggest that: first, hyperferremia would not only dampen immune responses but equally encourage the proliferation and subsequent infection of many pathogenic microorganisms and, second, that relative hypoferremia would not only confer an additional layer of protection in areas with endemic diseases but fundamentally alter "new" optimal iron values within populations of the species *Homo* residing within those areas. Restricting dietary iron may have protected against infection in areas of high transmission or morbidity (Wander et al. 2009). This phenomenon might one day elucidate the prevalence of anemic conditions within geographical regions disproportionately targeted by iron-acquiring pathogens (Pittman et al. 2016). At least in some specific environmental conditions, anemia likely reflects adaptative responses to pathogen load, a notion strengthened by the high prevalence of covert iron deficiency across the globe (Denic and Agarwal 2007).

To conclude, the shift to agriculture initiated long-term tradeoffs in human health—one of which involves a biological tension between the need for iron to support cell-mediated immunity and the evolutionary pressure to limit iron availability in order to restrict pathogen growth (Wander et al. 2009). As past epidemiological transitions reshaped human societies, increasing their size, complexity, and pathogen regimes, iron deficiency may have emerged as a byproduct of these adaptations—reflecting a broader mismatch between past adaptation and modern

environmental conditions. Although the most efficient way to increase iron remains the consumption of red meat, this once-critical food source has now become detrimental to public health. This finding is not due to iron itself or to its direct biological or ecological effects—such as those on microbial activity or infection risk—but rather to the broader downstream consequences of large-scale red meat production, including contamination, diet-induced inflammation in humans, and substantial environmental degradation, as explored in the sections that follow.

## Red Meat and Infectious Disease

Pathogenic parasites specific to red meat include the helminthic parasites *Taenia solium* and *Taenia saginata, Trichinella spiralis*, and the protozoan parasite *Toxoplasma gondii*. Known bacterial infections, such as toxin-producing *E. coli* (particularly O157:H7), *Campylobacter*, *Listeria*, *Clostridia*, *Brucella*, *Salmonella*, and *Bacillus anthracis* also occur frequently due to the consumption of various raw/undercooked meats. A comprehensive list of all microbial (and viral) infections associated with red meat consumption is beyond the scope of this review, but we briefly describe the major parasites below. This extends the evolutionary argument about iron discussed above: increased human population density and closer proximity to domesticated animals favored GI parasitism. This increase in parasitic infections is believed to have led to elevated bleeding and iron loss from the GI tract, further exacerbating iron-deficient phenotypes.

Phylogenetic studies of the evolution of *Taenia* tapeworms have revealed their relatedness to two important African carnivores—lions and spotted hyenas—both having shared the ancestral landscape with our ancestors (Terefe et al. 2014). Today, the classic pork tapeworm that is transmitted among both humans and between humans and pigs is *T. solium*, a zoonotic tapeworm (cestode). Taeniasis, or tapeworm infection, occurs when humans consume raw or undercooked pork contaminated with cysticerci, the larval form of *T. solium* (García et al. 2003). Once ingested, the cysticerci undergo a process called evagination and attach themselves to the intestinal wall upon reaching the small intestine (García et al. 2003). Over a period of approximately two months, they mature into adult tapeworms and can grow to lengths exceeding 3 meters (Flisser 1994). Untreated, *T. solium* can result in a serious and potentially fatal disease known as cysticercosis (Del Brutto 2013). In cysticercosis, eggs give rise to larval worms that travel to various regions within the bodies of pigs and humans, including muscle, eye, and brain tissue, using the circulatory system as its highway, a process that leads to the formation of cysts (Flisser 1994; García et al. 2003; Del Brutto 2013). The primary concern in this context is invasion into the central nervous system that leads to neurocysticercosis (NCC; Garcia 2018). Based on conservative estimates at the turn of the century, NCC resulted in approximately 50,000 deaths per year and stood as the leading cause of acquired epilepsy worldwide, contributing to as much as 30% of the additional cases of epilepsy observed in developing regions (Garcia et al. 2005). Globally, NCC continues to be the prevailing cause for acquired epilepsy (Reddy and Volkmer 2017), although, at least in the United States, extensive facility-based case series studies have indicated that the number of deaths from NCC is relatively low, with a case-fatality rate of less than 1% (Sorvillo et al. 2007). Still, such facility-based studies, while offering valuable insights, come with substantial limitations and may potentially underestimate the impact of cysticercosis as a cause of death.

*T. saginata*, the classic beef tapeworm, is the most widespread large zoonotic tapeworm infecting humans today, with an estimated 60–70 million carriers worldwide (Andreassen 2010). Taeniasis, as it is referred to, is also transmitted in the form of cysticerci found in contaminated meat (previously called "measly beef"), similar in appearance to *T. solium*-infected muscle meat of pigs. Unlike *T. solium*, for which humans can serve as both definitive and aberrant intermediate hosts, humans are solely the definitive hosts for the adult *T. saginata* tapeworm. In this life cycle, sexual reproduction occurs in the human intestine, while bovines (e.g., cattle, buffaloes, and yaks) serve as the exclusive

intermediate hosts, harboring the larval parasitic cysticerci within their muscle tissues. Infection in humans occurs through ingestion of viable cysticerci, typically via consumption of raw or undercooked beef. Although partially cooked, smoked, or pickled beef may still carry infective cysticerci, the highest risk is associated with raw preparation such as steak tartare and similar dishes. This is supported by higher rates of taeniasis in countries such as Ethiopia and Argentina, where raw or lightly cooked beef is traditionally consumed (Heyneman 1996). Today, *T. saginata* also remains widely distributed across East, Southeast, and South Asia (e.g., China, Indonesia, Malaysia, Mongolia, Nepal, Philippines, South Korea, Thailand, and Vietnam; Eichenberger et al. 2020).

*T. spiralis* is a nematode and is most often acquired from eating infected pork and some other mammals. It is estimated to cause 10,000 cases of trichinellosis (also called trichinosis) annually (Gottstein et al. 2009), although the availability and accuracy of data can vary between regions. There is also significant underreporting of worldwide infection rates because trichinosis can be asymptomatic or cause mild symptoms that may not be recognized or reported (Murrell and Pozio 2011). Toxoplasmosis, yet another global zoonotic disease, is caused by the protozoan parasite *T. gondii*, which is highly prevalent in both humans and animals globally (Dubey 2021b). Nearly 30% of the human population carries *T. gondii*, yet clinical toxoplasmosis is relatively uncommon (Robert-Gangneux and Dardé 2012). When symptoms do occur, they tend to be mild and can resemble other conditions and the diagnosis may be delayed (Gaulin et al. 2020; Schumacher et al. 2021) or missed completely (Teutsch et al. 1979). Two primary sources of *T. gondii* infection are the consumption of raw or undercooked meat containing *T. gondii* tissue cysts and the ingestion of water or food contaminated with oocysts excreted by cats (or close contact with infected cats in general). It remains uncertain, however, whether the severity of clinical toxoplasmosis in humans is linked to the consumption of infected meat or oocyst-contaminated foods; infections caused by oocysts are believed to result in more severe disease compared to the ingestion of bradyzoites or tissue cysts (Dubey 2021a). As with *T. solium* infections, toxoplasmosis can cause serious illness in humans of all ages, and especially immunocompromised individuals (Schmidt et al. 2016; Wang et al. 2017) and neonates (Robert-Gangneux and Dardé 2012; Torgerson and Mastroiacovo 2013; Dubey et al. 2021).

A further example is the transmission of bovine spongiform encephalopathy (BSE), also known as mad cow disease, to humans by a single prion, a glycosylphosphatidylinositol (GPI)-anchored, cell-surface glycoprotein expressed in most tissues. A prion is not a microbe, but rather a type of "infectious" agent that consists of a mutated and misfolded protein (Collinge 2016). Unlike pathogenic organisms, prions lack genetic material such as DNA or RNA. One of the remarkable characteristics of prions is their ability to transmit their misfolded conformation from one protein to another, leading to a chain-like reaction of dysfunction once exposed. The accumulation of misfolded proteins is associated with several neurodegenerative diseases, such as Creutzfeldt-Jakob disease (CJD) in humans, BSE in cattle, scrapie in sheep and goats, chronic wasting disease in cervids (e.g., deer and elk), and transmissible mink encephalopathy in minks, feline spongiform encephalopathy in cats, and camel prion disease in dromedary camels (Collinge 2001; Babelhadj et al. 2018). Despite their rarity, numerous well-documented cases exist where the disease has crossed from cattle to humans via consumption of prion-rich beef. In humans, prion diseases typically lead to severe and progressive neurological symptoms over time, including loss of coordination, muscle wasting, headaches, insomnia, depression, dementia, general malaise, and ill-defined pain sensations (Wadsworth and Collinge 2007).

## Known Disease Associations with Red Meat Consumption: The Situation Today

With the many strides made in medical care throughout the last century, including the development of life-saving vaccines and

antibiotics and improved access to clean drinking water and better sanitation, once widespread infectious diseases have declined significantly. Notwithstanding these efforts, the 20th century also witnessed the emergence of "diseases of civilization," diseases directly attributed to lifestyle (e.g., smoking, insufficient physical activity, and chronic stress) and dietary factors (e.g., overnutrition, lack of dietary fiber, and altered eating habits). The mismatch between our ancestral physiology and the modern lifestyle/diet appears to be an underlying driver and widespread pathogenesis of coronary heart disease, obesity, hypertension, type 2 diabetes mellitus (T2DM), osteoporosis, and some epithelial cell cancers and autoimmune diseases (Carrera-Bastos et al. 2011)—all conditions that appear to be rare in present-day hunter-gatherer societies.

Between 1990 and 2022 the global rates of underweight status have dramatically diminished while obesity rates have increased significantly in all societies (NCD Risk Factor Collaboration 2024). Although the incidence of these chronic conditions also rises with longevity and, with respect to red meat consumption, it is particularly difficult to pinpoint known disease associations as it relates to early hominins. Computerized tomography scans of mummies from four different populations, spanning 4000 years, famously demonstrated atherosclerosis in preindustrial agricultural populations (Thompson et al. 2013), a condition commonly associated with red meat intake today (Micha et al. 2012; O'Connor and Campbell 2017). However, it is thought that the elevated inflammatory exposure resulting from infection largely contributed to the development of coronary artery disease (CAD) in these populations (Abd et al. 2011). Setting aside the small numbers in this study and the incongruence of evidence from prior studies (Vasunilashorn et al. 2010; Allam et al. 2011; Gurven et al. 2012; Singh et al. 2013; Thompson et al. 2013; Bedi et al. 2014), the true incidence of the many "diseases of civilization" in Paleolithic hunter-gatherers is challenging to estimate. Data from populations with preindustrial diets and lifestyles—engaging in activities such as hunting, gathering, fishing, and farming—consistently show minimal incidence of CAD, despite high exposure to infectious and inflammatory stressors. This implies that CAD is largely preventable in individuals who consistently maintain metabolic profiles characteristic of contemporary forager populations, including lean body composition (i.e., "normal BMI"), low blood pressure, low LDL cholesterol, stable glucose regulation, abstinence from smoking, and regular physical movement (Kaplan et al. 2017). Both CAD and carcinomas appear to be rare in captive chimpanzees (Varki et al. 2009, 2011; Varki and Varki 2015), suggesting that humans may have evolved an increased susceptibility to these diseases under modern environmental conditions. Although red meat consumption is actively studied in relation to chronic disease (Larsson and Orsini 2014; Alisson-Silva et al. 2016; Ekmekcioglu et al. 2018; Pan et al. 2022; Li et al. 2025; Ungvari et al. 2025), specific health risks are difficult to pinpoint because they vary with factors such as intake frequency, meal composition, animal source, and methods of raising, preparing, and processing. Importantly, participants in studies with low versus high intake of red meat often exhibit differential characteristics, with those who consume more tending to have an overall poorer diet quality, higher BMI, reduced physical activity, lower education level, and greater prevalence of smoking (Maki et al. 2014). As a result, confounding factors closely associated with red meat consumption and the incidence of atherosclerosis (among others) will consistently challenge strong association claims, raising doubts about any causality. Nevertheless, the most robust and reliable diet data set derived today comes from large-scale cohorts, especially the Health Professionals Follow-up Study (HPFS, since 1986), Nurses' Health Study I (NHS I, since 1976), Nurses' Health Study II (NHS II, since 1989), National Institutes of Health-AARP (NIH-AARP, formerly known as the American Association of Retired Persons) Diet and Health Study, and the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Most published data from these cohorts are derived from tens of thousands of individuals and, in some cases,

close to half a million individuals (e.g., NIH-AARP and EPIC cohorts).

The largest categories of chronic diseases associated with red meat consumption are cardiovascular disease (CVD; a broad classification that includes atherosclerotic CAD, myocardial infarctions, stroke, and hypertension), carcinomas (cancers of epithelial tissues, including surface and glandular epithelia), and T2DM (a metabolic and endocrine disorder characterized by insulin resistance and hyperglycemia). These diseases are now among the leading causes of death worldwide. The definition of "processed" meat differs slightly between many studies but includes products that are preserved by methods other than freezing, such as salting, smoking, marinating, heating, and drying. This includes products such as sliced ham, bacon, sausage, hamburger, salami, corned beef, tinned meat, beef jerky, and so on (Linseisen et al. 2002).

Large meta-analyses show recurrent and strong associations between red meat and T2DM (Zhang et al. 2021, 2023; Yu et al. 2023; Li et al. 2024), as well as multiple forms of CVD (de Medeiros et al. 2023; Shi et al. 2023; Wang et al. 2024). Importantly, these studies demonstrate a dose-response relationship between red meat and disease, while also showing a clear worsening association with processed over unprocessed red meat.

This theme further extends to carcinomas, particularly colorectal cancer (CRC). Recent meta-analyses show strong associations between beef, lamb, pork, and other mammalian meat and CRC (Carr et al. 2016), T2DM (Aune et al. 2009; Micha et al. 2012), stroke (Bechthold et al. 2019), coronary heart disease (CHD; Micha et al. 2012; Bechthold et al. 2019), heart failure (Bechthold et al. 2019), obesity (Rouhani et al. 2014), and all-cause mortality (Larsson and Orsini 2014; Etemadi et al. 2017).

The International Agency for Research on Cancer has classified processed meat as "carcinogenic to humans" (Group 1) and red meat as "probably carcinogenic to humans" (Group 2A; Bouvard et al. 2015). A large body of evidence indicates that CRC risk increases with higher consumption of red meat, with the risk being consistently greater for processed red meat. For example, CRC incidence increases by 17% with daily consumption of 100 g of total red meat (processed and unprocessed), and by 18% with just 50 g per day of processed meat alone (Chan et al. 2011). These associations have been consistently confirmed in multiple meta-analyses across both men and women for unprocessed, processed, and total red meat intake (Zhao et al. 2017; Farvid et al. 2021; Papier et al. 2025; Ungvari et al. 2025).

These analyses have linked red and processed red meat consumption to increased incidence and mortality risk for a range of cancers beyond CRC, including non-Hodgkin lymphoma (NHL), bladder, breast, endometrial, esophageal, gastric, lung, and nasopharyngeal cancers (Farvid et al. 2021; Huang et al. 2021). Processed meat intake has been associated with elevated overall cancer mortality risk, especially for NHL, bladder, breast, colorectal, esophageal, gastric, nasopharyngeal, oral cavity, oropharyngeal, and prostate cancers. These associations show a clear dose-response relationship: for every 100 g per day of red meat, the risk of various cancers increases by 11–51%, and for every 50 g per day of processed meat, the risk increases by 8–72% (Huang et al. 2021).

The overall evidence is convincing enough for the World Cancer Research Fund and American Institute for Cancer Research to recommend limited consumption of red meat and avoidance of processed meat altogether (Wiseman 2008). The stance from the most recent U.S. Dietary Guidelines is markedly different, however, recommending increased protein intake and omitting any explicit recommendation to avoid processed meat (Mozaffarian 2026).

### Red Meat Increases All-Cause Mortality

The association between red meat with cancer and CVD translates to increased overall mortality (Wang et al. 2016). In CRC studies, prediagnostic intake of red and processed meat was associated with greater all-cause

mortality—and those with highest intake of red and processed meat were at greater risk of CRC-specific mortality (McCullough et al. 2013). Data from the NIH-AARP cohort indicate that men and women in the highest quintile of red and processed meat intake had an elevated risk of overall and cancer morality (Sinha et al. 2009). Adherence to a "Western" dietary eating pattern—characterized by high intakes of red and processed meats, high-fat dairy products, refined grains, fried or processed foods, desserts, and sugar-sweetened beverages—after a CRC diagnosis has been associated with increased recurrence and mortality (McCullough et al. 2013). As observed in the American Cancer Society's Cancer Prevention Study II (CPS II), those who specifically consumed the highest amount of red meat, both pre- and postdiagnosis, were more likely to develop CRC again after resection (McCullough et al. 2013); in a smaller U.S. study, postdiagnosis red meat intake was associated with higher mortality risk, but only among those with a familial history of CRC (Zell et al. 2007).

A prospective analysis conducted using the HPFS for men and the NHS for women examined the relationship between red meat consumption and mortality from both cancer and CVD (Pan et al. 2012). Even after adjusting for major lifestyle and dietary risk factors, there existed a linear dose response. The pooled hazard ratio of total mortality was 1.13 for one serving a day increases for fresh red meat (85 g per day) and 1.2 for processed red meat. The corresponding hazard ratios were 1.18 and 1.21 for CVD mortality and 1.10 and 1.16 for cancer mortality, respectively. Substituting one serving of meat per day with other plant-based foods was estimated to lower mortality risk by 7–19%, and that 9.3% of deaths in men and 7.6% in women in could be prevented if all individuals consumed fewer than 0.5 servings per day.

Although we regard the cumulative epidemiological evidence as conclusive in linking red meat consumption with CVD, certain cancers, and all-cause mortality, we, like others, also emphasize the limitations of such studies, noting that risk estimates are far from uniform across populations—particularly those with traditionally low intake or where red meat consumption has only recently risen (Lee et al. 2013; Abete et al. 2014; Wang et al. 2016). This variation in disease risk and mortality reflects inevitable inconsistencies arising from factors such as the quantity and duration of red meat consumption (Abete et al. 2014; Wang et al. 2016), insufficient differentiation between processed and unprocessed forms (Snowdon et al. 1984; Mann et al. 1997; Fraser 1999; Abete et al. 2014), the degree of confounding control (Mann et al. 1997; Abete et al. 2014) and, notably, differences in the comparison sources of dietary energy (Whiteman et al. 1999; Abete et al. 2014; Zeraatkar et al. 2019; Zhong et al. 2020). In many populations, intake of refined starches, sugar, potatoes, and fats (that are either highly saturated or partially hydrogenated) are primary sources of energy. Because diet is rarely measured before diagnosis, it is uncertain whether reported intake reflects long-term habits or recent changes, and much of what is categorized as a "Western" dietary pattern includes not only red and processed meats but also roughly equal contributions from dairy products, refined grains, condiments, and desserts. Consequently, analyses that do not explicitly specify the comparison foods are effectively pitting red meat against these less-than-ideal sources of energy intake. In this context, the absence of an association between red meat and disease outcomes simply indicates that red meat is no healthier than the suboptimal foods to which it is being compared.

Despite differences in pathogenic mechanisms and familial risk factors, the diseases described above share a unifying feature: all are aggravated by *chronic inflammation.* Finally, increasing attention has been given to mammalian meat allergy, also known as alpha-gal syndrome, a condition triggered by tick bites that sensitize individuals to the carbohydrate galactose-α-1,3-galactose (alpha-gal), abundantly present in red meat. Alpha–gal is a terminal galactose residue linked to an underlying glycan via an α1–3 glycosidic bond. This molecular bond is highly antigenic to humans and all other Old World primates due to the fact that these species have long lost the function of the enzyme that synthesizes this type of glycosidic linkage (Galili

2023). As a result, most humans have large amounts of circulating anti–alpha-gal IgG antibodies. Upon a bite by a lone star tick (*Amblyomma americanum*) in North America or a castor bean tick (*Ixodes ricinus*) in Europe, the saliva of the tick, containing salivary proteins that bear alpha-gal molecules, causes further sensitization. This exposure induces an IgE-mediated immune response, such that subsequent ingestion of commonly consumed sources of red meat may provoke strong allergic reactions to alpha-gal including, in severe cases, anaphylactic shock (Commins and Platts-Mills 2013; Contreras et al. 2023; Ross et al. 2025).

## Proposed Mechanisms by Which Red Meat Contributes to Chronic Disease

Numerous mechanisms have been proposed to explain the association between red meat intake and chronic disease. In analyzing various claims, it is critical to note that the same disease associations are generally not seen for poultry and fish consumption, and that habitual carnivores do not all share the same risks. Experimental evidence indicates that meat-preserving nitrite/nitrate curing salts and their byproducts could potentially decrease insulin production, impair glucose tolerance (Srour et al. 2023), promote endothelial dysfunction and atherosclerosis (Förstermann 2008), or even directly contribute to diabetes (Gajdosík et al. 1999). Nitrite treatment of red meats also leads to the formation of potentially carcinogenic nitrosamines when consumed (Jakszyn and González 2006). However, similar preservatives are often used in nonred meats, and epidemiological and human studies are currently lacking. In a similar vein, the many reports connecting proven mutagens and carcinogens produced by the grilling of red meats—the *N*-nitroso compounds, heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) and their alkylated derivatives—are confounded by the production of the same molecules during grilling, roasting, barbecuing, smoking, and preserving of nonmammalian meats (e.g., fish and poultry; Knekt et al. 1999; Lijinsky 1999; Phillips 1999; Sugimura et al. 2004; Viegas et al. 2012; Gibis 2016). Furthermore, the amount needed to induce cancers in rodents are 1000 to 100,000 times greater than the levels typically present in cooked meat products (Stavric 1994; Schwab et al. 2000). Given these challenges, and the persistent quest for technological solutions to mitigate the deposition or synthesis of these compounds in food (Onopiuk et al. 2021), popular media continues to report on these possibilities, a sentiment further echoed by many national and international public health agencies (Bouvard et al. 2015).

Other factors contributing to the inflammatory nature of red meat consumption are better supported by the available evidence. Increased saturated fat and cholesterol from red meat may explain the association of the increased risk of CHD and stroke, given their known mechanistic role in atherogenesis. The high sodium content of processed red meat can also modestly contribute to CVD mortality through its dual effects of increasing blood pressure (He and MacGregor 2002) and of worsening of arterial compliance (Sanders 2009). Excess intake of heme iron, too, possibly increases free radical production and oxidative DNA damage in the GI tract, which gives credence to the association between its intake with colon cancer (Bastide et al. 2011). Yet, given the very high levels of the heme-binding protein hemopexin in plasma, it is difficult to see how the heme would ever reach the coronary arteries to potentiate myocardial infarction and CHD (Ascherio et al. 1994; Klipstein-Grobusch et al. 1999; van der A et al. 2005). It has also been proposed that intestinal microbiota can generate the proatherogenic compounds trimethylamine *N*-oxide (TMAO) and its derivative trimethylamine (TMA) from nutrients found within mammalian meat (Wang et al. 2011; Koeth et al. 2013; Tang et al. 2013; Ufnal et al. 2015; Chen et al. 2017; Zeisel and Warrier 2017), which is linked to increased risks of CVD and higher all-cause mortality (Gruppen et al. 2017; Roberts et al. 2018). However, this mechanism is not specific to red meat consumption. The key precursor molecules to TMAO and TMA production—carnitine, phosphatidylcholine

(lecithin), choline, and betaine—are widely distributed in other foods (Rohrmann et al. 2016). Carnitine, lecithin, and choline are plentiful in saltwater fish, milk, cheese, and eggs (Weihrauch and Son 1983; Demarquoy et al. 2004; Zeisel and da Costa 2009), whereas betaine is found in wheat bran, wheat germ, spinach, beets, and shellfish (Likes et al. 2007). Because these are essential nutrients, it is possible that the conversion of choline and carnitine into TMAO is contingent on the equilibrium and, quintessentially, diversity of the gut microbiota. Disturbed microbial composition of the GI tract may directly result in elevated plasma TMAO levels, possibly contributing to the development of atherosclerosis (Rak and Rader 2011; Wang et al. 2011; Brown and Hazen 2015; Chhibber-Goel et al. 2017; Zhen et al. 2023). Any one of the aforementioned processes should apply to other mammalian species, but many of these risks are hard to reproduce in animal models and are not obvious in other habitual carnivores. Like human trials, studies conducted in animals suggest that advanced age must be considered a relevant factor when investigating "diseases of civilization" (Brunt et al. 2019). Large epidemiological and human studies are not available for most of these proposed mechanisms and conclusive proof of causation remains elusive.

Unlike the examples mentioned above, one uniquely human mechanism involves the loss of an evolutionarily common type of sialic acid in our species (Dhar et al. 2019). Sialic acids are a diverse family of nine-carbon backbone amino sugars that serve as terminal residues on glycan chains of cell-surface and secreted glycoconjugates (including glycoproteins and glycolipids) in all vertebrates. These sugars are highly abundant, with tens to hundreds of millions of sialic acid molecules decorating the surface of every vertebrate cell (Varki 2007). Their location at the outermost layer of the cell membrane makes them essential players in a wide range of biological and physiological processes: cellular communication, development, immune recognition, and interactions with microbes (Varki 2007). The two major types of sialic acids on the glycan coat of mammalian cell surfaces (i.e., the glycocalyx) are *N*-acetylneuraminic acid (Neu5Ac) and *N*-glycolylneuraminic acid (Neu5Gc); the latter is synthesized from the former by an enzyme called cytidine monophospho *N*-acetylneuraminic acid hydroxylase (CMAH). The loss of function of the *CMAH* gene in the hominin lineage occurred approximately 2 mya, well after humans diverged from the great apes (an evolutionary split estimated at 6–7 mya; Figure 3), and appears to have undergone rapid fixation (Hayakawa et al. 2001; Ghaderi et al. 2011; Altman and Gagneux 2019). Although humans are unable to synthesize Neu5Gc, this nonhuman sialic acid is abundant in the tissues of many other mammals commonly consumed by humans, making dietary exposure to Neu5Gc an ongoing, relevant, and global phenomenon. Neu5Gc is found in highest amounts in beef, pork, and lamb (Samraj et al. 2015). Amounts of Neu5Gc vary between several cattle breeds and even between different parts of their bodies (Contò et al. 2025). Neu5Gc has also been detected in a few select fish and marine invertebrates (Samraj et al. 2015), including salmon eggs and sea urchins. Neu5Gc is absent in all plant foods, as well as all poultry. Unlike in the case of the antigenic alpha-gal also missing in humans and discussed above, where the antigenic nature of the molecule lies in the type of glycosidic linkage and not in the terminal galactose monosaccharide itself, the terminal monosaccharide Neu5Gc is directly antigenic. Alpha-gal epitopes are metabolized into free galactose and humans are incapable of regenerating the antigenic alpha-gal epitope.

In contrast, individuals who consume Neu5Gc-rich food metabolically incorporate this animal sialic acid into secreted glycoproteins and cell surface glycoconjugates, including on endothelial and epithelial glycocalyces throughout the body (Tangvoranuntakul et al. 2003; Chappell et al. 2009). After the discovery of Neu5Gc in human tissues, it was assumed that metabolically incorporated Neu5Gc from the diet provided the initial stimulation for anti-Neu5Gc antibody formation, but current evidence suggests otherwise (Taylor et al. 2010; Samraj et al. 2015; Altman and Gagneux 2019). We have shown that early life exposure

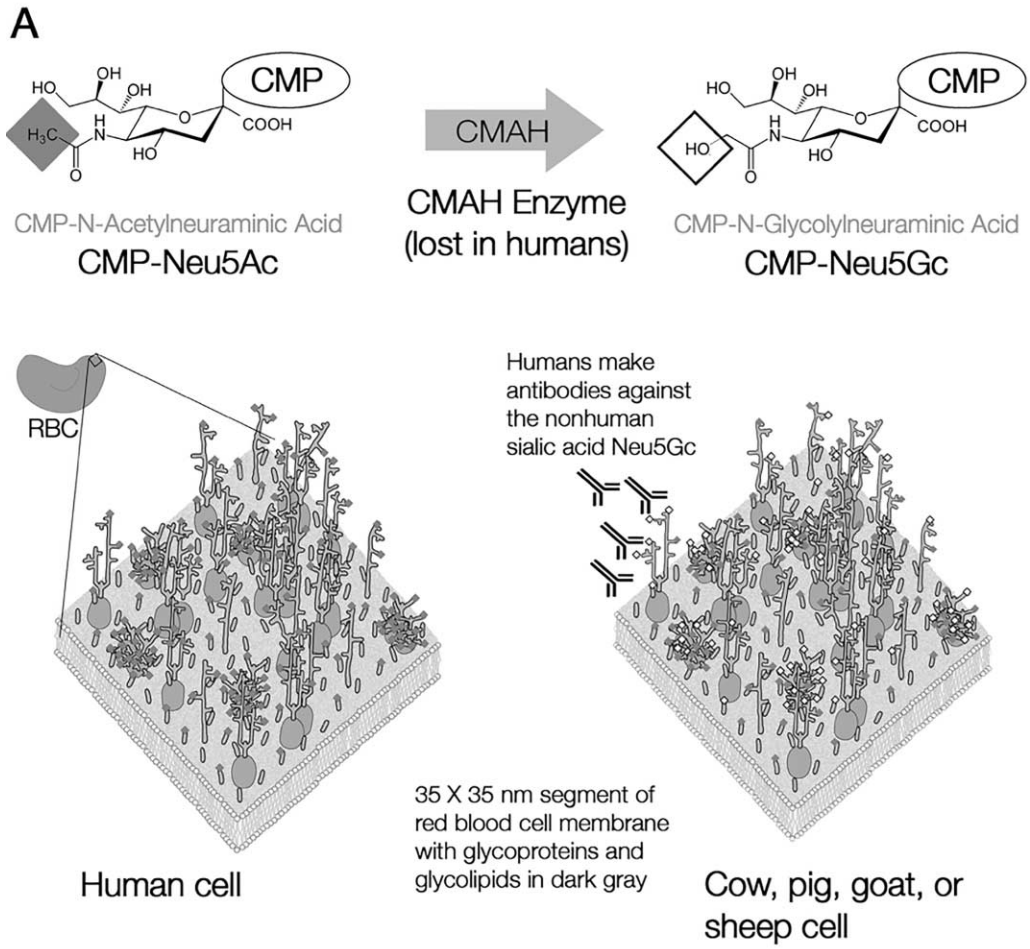


Figure 3. Sialic Acid Differences in Humans Versus Most Red Meat-Providing Animals

Human cell surfaces underwent a watershed evolutionary shift approximately 2–3 million years ago, due to the fixation of a recessive loss-of-function mutation in the *CMAH* gene (Altman and Gagneux 2019). This mutation eliminated the ability to convert Neu5Ac into Neu5Gc, resulting in a unique human physiology: cells that lack endogenous Neu5Gc (and, thus, carry only Neu5Ac) and an immune system that produces antibodies against Neu5Gc-containing structures. The immune system can detect trace amounts of animal-derived Neu5Gc when they become metabolically incorporated through the diet. Additionally, the lack of a single oxygen atom in Neu5Ac compared to Neu5Gc has significant implications for hydrophobicity, binding affinity, and molecular interactions—demonstrating how even subtle molecular changes may have profound and still poorly understood effects on molecular recognition and biological function (Dunker et al. 2025). Redrawn Figure 1 from Altman and Gagneux (2019). Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

to nontypeable *Haemophilus influenzae* (NTHi) can take up free Neu5Gc from its surrounding environment, primarily from dietary sources, and metabolically incorporate it into its lipopolysaccharides. The microbial display of Neu5Gc is thought to initiate an early life immunization, leading to the production of anti-Neu5Gc antibodies (Taylor et al. 2010). Although the exact timing of their appearance and mechanism for their formation

remain unclear, these antibodies persist and their levels remain relatively stable into adulthood, with considerable variation in levels between individuals (Zhu and Hurst 2002; Tangvoranuntakul et al. 2003; Samraj et al. 2018). Hence, metabolic incorporation of dietary Neu5Gc, in the face of preexisting anti-Neu5Gc antibodies, sets up a diet-mediated inflammatory process we have termed "xenosialitis" (Dhar et al. 2019). As Neu5Gc is found in high levels in red meat, ongoing consumption may give rise to persistent antigen-antibody complexes, resulting in low-grade chronic inflammation that possibly underpins the high frequency of diet-related atherosclerosis, carcinoma, and other diseases of medical relevance today (Padler-Karavani et al. 2008; Liang et al. 2024).

Among the various diseases associated with endothelial inflammation, atherosclerosis is among the most widespread, characterized by an intimal buildup of LDL cholesterol and oxidized lipids—a process itself exacerbated by both metabolic and immune-mediated factors. Building on evidence that dietary Neu5Gc promotes plaque development, histological staining using an affinity-purified polyclonal chicken anti-Neu5Gc IgY—the most specific antibody available for detecting Neu5Gc-containing glycoconjugates—has revealed accumulation of Neu5Gc within the vascular endothelium overlying atherosclerotic lesions in human diseased tissues (Figure 4A; Pham et al. 2009). These sites also exhibited increased infiltration of $CD68^+$ macrophages and immunoreactivity for the lipid peroxidation marker malondialdehyde (MDA; Figure 4A), indicating that Neu5Gc incorporation, even in trace amounts, may enhance local oxidative stress and immune cell recruitment (Pham et al. 2009). Moreover, in mice models with "human-like" mutations in the sialic acid modifying enzyme and LDL receptor ($Cmah^{-/-}Ldlr^{-/-}$), accelerated atherosclerosis occurs when they are fed a high-fat diet (HFD) supplemented with Neu5Gc-rich mucin—mimicking red meat consumption—in the presence of anti-Neu5Gc antibodies (Kawanishi et al. 2021). Although $Cmah^{-/-}Ldlr^{-/-}$ mice fed a HFD without Neu5Gc exhibited some plaque development, those fed an equivalent HFD enriched with Neu5Gc developed more extensive atherosclerotic lesions (Figure 4B). Importantly, Kawanishi et al. (2021) note that Neu5Gc promotes vascular inflammation and lesion growth, independent of changes in body weight or plasma cholesterol levels (Kawanishi et al. 2021).

New findings extend this concern to epithelial tissues of the intestinal tract (Lopes et al. 2025) have shown that a Neu5Gc-enriched diet leads to the development of intestinal polyps with more malignant features in $Cmah^{-/-}$ mice. Moreover, when incorporated into CRC cells, Neu5Gc was found to activate the Wnt/β-catenin signaling pathway, an essential driver of cell proliferation and tumorigenesis. Neu5Gc incorporation into intestinal cells was associated with increased expression of Wnt target genes, suggesting a tumor-promoting mechanism independent of immune-mediated inflammation. Consistent with these findings, Neu5Gc-containing glycoconjugates have been shown to preferentially accumulate in malignant tumors (likely driven by dietary uptake, hypoxia, and metabolic shifts), where they contribute to the activation of oncogenic pathways and may serve as prognostic markers or therapeutic targets (Hedlund et al. 2008; Blanco and Muñoz 2025). These findings offer novel insights into how red meat consumption may directly influence CRC progression through Neu5Gc-driven activation of oncogenic signaling pathways.

Together, these observations support a human-specific state in which dietary Neu5Gc not only integrates into some tissues but also contributes to the inflammatory microenvironment that drives plaque formation. In alignment with this mechanistic insight, existing dietary guidelines for the prevention of chronic diseases (Krauss et al. 2001; Kushi et al. 2006; Reedy and Krebs-Smith 2008; Wiseman 2008; Bouvard et al. 2015; Willett et al. 2019; Li et al. 2024) consistently recommend limiting red and processed meat consumption in favor of predominantly plant-based foods, as well as certain fish and poultry.

Recently, a study by Li et al. (2025) found that higher intake of red meat, particularly processed red meat, was associated with an increased risk of cognitive decline and

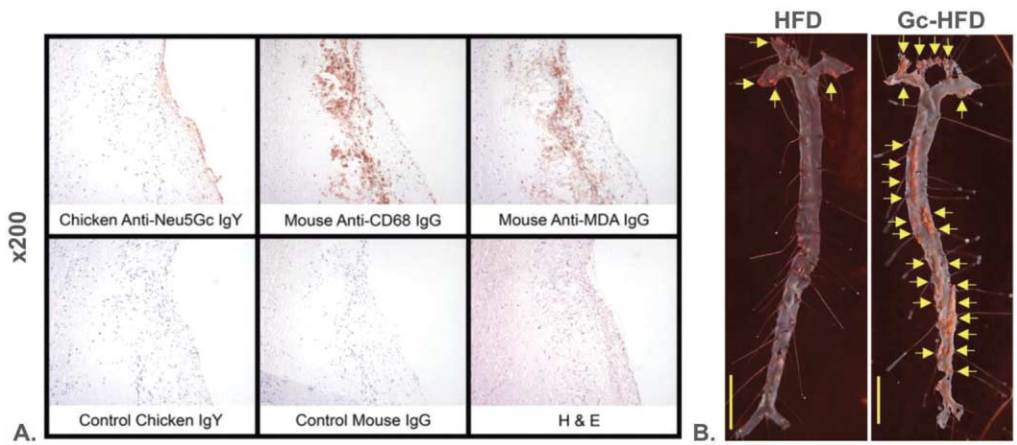


Figure 4. Presence of *N*-Glycolylneuraminic Acid (Neu5Gc) in Atherosclerotic Plaques of Humans and Mice

(A) Representative sections of human aortic atherosclerotic plaques. Immunohistochemical analysis shows infiltration of macrophages (anti-CD68, *top middle*) and oxidized LDL particles (malondialdehyde, *top right*). Neu5Gc was detected on the endothelium overlying plaques using chicken-derived anti-Neu5Gc IgY (*top left*). Negative controls using nonimmune chicken IgY and mouse IgG (*bottom left and bottom middle, respectively*) confirm staining specificity. H&E (hematoxylin/eosin) staining indicates general histology (*bottom right*; Pham et al. 2009). (B) En-face imaging of atherosclerotic plaques in *Cmah*$^{-/-}$*Ldlr*$^{-/-}$ mice (indicated by light arrows) compares two dietary interventions—a standard high-fat diet (HFD) and a Neu5Gc-enriched high-fat diet (Gc-HFD)—in a genetically humanized atherosclerosis-prone model. These mice mimic both the human-specific loss of *CMAH* and the elevated cardiovascular risk associated with high LDL levels, allowing a more relevant investigation of red meat-driven vascular inflammation (Kawanishi et al. 2021). Images of Neu5Ac-fed control mice are not shown but were included in the original analysis as a dietary baseline. Figure 4A was originally published in *Blood* (Pham et al. 2009:Figure 5B), ©the American Society of Hematology. Figure 4B was reprinted with permission from Kawanishi et al. 2021:Figure 1b.

dementia (Li et al. 2025). As shown above, one of the prominent sites of Neu5Gc incorporation is the endothelium, which includes the endothelium of cerebral blood vessels. The inflammatory effects of Neu5Gc accumulation have been demonstrated in human endothelial cells, where incorporation enhances cytokine release, complement activation, and selectin expression (Hedlund et al. 2008)—hallmarks of vascular inflammation and well-established factors for dementia (Zuliani et al. 2008; Tian et al. 2022; Nimmo et al. 2024). Persistent low-grade inflammation, exacerbated by xenosialitis, could impair endothelial integrity and contribute to neuroinflammation. The same xeno-autoantigen/xeno-autoantibody response that promotes endothelial dysfunction in CVD may also be relevant to cerebral small vessel disease, a recognized contributor to vascular dementia (Sierra 2012; Rincon and Wright 2014; Rensma et al. 2018; Wardlaw et al. 2019; Jacob et al. 2023). Our previous work has demonstrated that systemic inflammatory markers—including IL-6, serum amyloid A, and haptoglobin—are elevated in atherosclerosis (Samraj et al. 2015). These same markers are also elevated in Neu5Gc-fed *Cmah*$^{-/-}$ mice given passively transferred anti-Neu5Gc antibodies. Thus, the link between red meat consumption and cognitive decline may not only be a function of saturated fat intake or other dietary factors, but also a direct consequence of Neu5Gc-driven inflammation at the neurovascular interface.

An alternative hypothesis proposes that *CMAH*$^{-/-}$ human cancer cells may generate small amounts of Neu5Gc endogenously

through oxidative stress (Bousquet et al. 2018), a conversion that could be achieved in vitro only under very harsh chemical conditions (Bai et al. 2023). Elevated reactive oxygen species are claimed to cause limited Neu5Gc formation from Neu5Ac in vivo (Shewell et al. 2018, 2022; Wang et al. 2023a). Although intriguing, this mechanism lacks direct biochemical validation and is not mutually exclusive with more widely supported explanations, such as dietary incorporation or NTHi-induced immunization against Neu5Gc-containing glycans.

Given the breadth and complexity of this topic alone, it is not feasible to cover each proposed mechanism in detail within the scope of this review. However, Table 1 provides a concise summary of the major hypotheses linking red meat consumption to carcinoma risk, along with brief descriptions of their underlying mechanisms.

## Environmental Impacts of Red Meat Production

The inefficiency in the conversion of energy captured through photosynthesis into large ruminant tissue explains why the consumption of red meat is an environmentally and energetically expensive process. Nearly 40% of the world's grain is cultivated to produce livestock feed rather than for direct human consumption (Ornish 2012). Although the global expansion and mass production of red meat may be seen as a technological feat in the story of *Homo*, the extensive scale of livestock farming appears to be approaching its limits, facing constraints imposed by its own expansion. Such intensive rearing practices have resulted in the degradation of terrestrial and aquatic ecosystems, depletion of water resources, and exacerbation of a warming climate (Godfray et al. 2010; Foley et al. 2011; Godde et al. 2021).

The production and consumption of meat is linked to anthropogenic climate change, with three major GHGs propelling significant atmospheric alterations: first, $CO_2$, from the conversion of forests to grasslands, cultivation of feed crops, and the energy used to fertilize, harvest, and transport products; second, $CH_4$, from the enteric fermentation and manure management of ruminants; and, finally, $N_2O$, from synthetic fertilizer application, use of nitrogen-fixing crops, and the nitrification and denitrification of ruminant wastes on rangelands (Masson-Delmotte et al. 2021). These three GHGs contribute to 80% of today's gross warming (46%, 29%, and 5%, respectively), reinforcing the notion that agriculture is responsible for the commonly cited 15–20% of current warming levels. Curiously, within the nationally determined contributions to the Paris Agreement, only one-third of countries make reference to mitigation measures associated with agriculture (Rose et al. 2021).

Compared to plant-based food sources, beef and lamb production have much higher GHG emissions as $CH_4$ is a potent GHG that has an atmospheric life span of 10 or more years, unlike $CO_2$, which can persist for hundreds of years—and $N_2O$ lasts a century (Masson-Delmotte et al. 2021). Among these gases, $CH_4$ emissions have driven a remarkable amount of heating, with estimates ranging from around 23% to 40% of the total global warming (Myhre et al. 2013; Etminan et al. 2016). The estimate may even be higher when considering feedback processes on other radiative forcings allowing $CH_4$ to influence its own life span and that of $CO_2$ (i.e., $CH_4$ is involved in ozone production and, when oxidized in the troposphere, $CO_2$ is produced as a synergistic byproduct and further increases atmospheric GHGs; Myhre et al. 2013). Hence, estimating the warming impact of the agriculture sector is a rather formidable task since it emits multiple GHGs with widely varying radiative properties—emanating from millions of different sources—each with their own atmospheric longevity (Lynch et al. 2021; Masson-Delmotte et al. 2021).

Moreover, waste generated by extensive feeding operations has become a major contributor to environmental pollution (Crane et al. 1983; Baxter-Potter and Gilliland 1988; Barker and Zublena 1995; Boxall et al. 2003; Weldon and Hornbuckle 2006; Spellman and Whiting 2007; Heaney et al. 2015; Mallin et al. 2015). Waste often seeps into groundwater or directly contaminates entire watersheds during rainfall (Burkholder et al. 1997, 2007;

TABLE 1

*Possible connections between red meat intake and carcinoma risk in humans*

| Hypothesis | Proposed mechanisms | Supporting evidence | Conflicting/unsupportive evidence |
|---|---|---|---|
| **Nitrites and *N*-nitroso compounds (NOCs)** | Alkylating agents that cause DNA damage<br>Endogenously formed via heme-catalyzed *N*-nitrosation in the colon (heme iron markedly increases fecal NOCs; Mirvish 1995; Bingham et al. 2002; Cross et al. 2003)<br>Exogenously formed during processing of red meat (Santarelli et al. 2008) | NOCs induce oncogenic mutations in rodents (Jacoby et al. 1992)<br>Human studies: dose-dependent correlation between red meat intake and fecal NOC levels (Bingham et al. 1996, 2002; Joosen et al. 2009) | Proposed mechanism is not specific to red meat, as deli meats such as chicken and turkey can contain added nitrates and nitrites<br>NOCs do not initiate precancerous lesions in rodents, even with added carcinogens (Parnaud et al. 2000)<br>No consistent epidemiological link between red meat-derived NOCs and overall carcinoma risk |
| **Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs)** | Produced during high-temperature cooking (grilling, smoking, barbecuing) of red meat<br>HCAs: formed by pyrolysis of creatine plus amino acids<br>PAHs: formed by incomplete combustion of organic material<br>"Grilling hypothesis": cooking method may drive carcinogenic exposure | HCAs are mutagenic and carcinogenic in animal models (Adamson et al. 1996)<br>PAHs form DNA adducts (O'Neill et al. 1991; World Health Organization International Agency for Research on Cancer 1994; Choi et al. 2010)<br>Epidemiological studies link cooking method with cancer risk (Zheng and Lee 2009) | Proposed mechanism is not specific to red meat, since HCAs/PAHs are also generated by poultry and fish; epidemiological findings are inconsistent, with fish intake sometimes linked to protective effects (Caini et al. 2022)<br>Rodent/monkey doses required for carcinogenesis = 1000–100,000 times higher than human dietary exposure (Stavric 1994) |
| **Heme iron** | Catalyzes endogenous *N*-nitrosation (Cross et al. 2003)<br>Promotes lipid peroxidation, generating carcinogenic aldehydes (Bastide et al. 2011)<br>Direct cytotoxic/hyperproliferative effects (Sesink et al. 1999) and iron-driven hypoxia signaling (Huang 2003) | Animal studies show dietary heme enhances carcinogenesis (Pierre et al. 2003)<br>Epidemiological studies report increased CRC risk with higher heme intake (Bastide et al. 2011)<br>Multiple mechanisms may act synergistically to promote tumorigenesis, e.g., HCAs are activated by heme iron (Lakshmi et al. 2005) | Proposed mechanism is not specific to red meats; poultry contains heme iron; and iron content in marine and freshwater species varies widely by taxon, species, and muscle type<br>No single mechanism adequately explains observed associations (Clinton et al. 2020)<br>Large meta-analysis found only weak links between heme intake and cancer risk (Fonseca-Nunes et al. 2014)<br>Effects appear site-specific (colon/rectum) rather than systemic |
| **Total fat and bile salts** | Red meat contributes to high levels of saturated fats<br>High-fat diets stimulate bile acid secretion; secondary bile acids can be carcinogenic in the GI tract<br>Altered bile acid metabolism may influence gut microbiota composition and tumor promotion | Early animal and epidemiological studies link high-fat diets to CRC development<br>Bile acids shown to modulate tumor-related signaling and immunity (Cong et al. 2024) | Proposed mechanism is not specific to red meat; poultry/fish have fat and stimulate bile acid release<br>Epidemiological evidence inconsistent across populations<br>Limited to no conclusive association between total fat intake and CRC (Clinton et al. 2020)<br>CRC risk from red meat intake persists after adjusting for fat intake |

TABLE 1
*Continued*

| Hypothesis | Proposed mechanisms | Supporting evidence | Conflicting/unsupportive evidence |
|---|---|---|---|
| **Metabolic dysregulation (insulin resistance/ IGF-1 axis)** | Red meat is often consumed with refined carbohydrates and saturated fats; chronic excess caloric intake promotes obesity and visceral adiposity, which impair insulin signaling<br>Hyperinsulinemia and insulin resistance (IR) elevate circulating insulin and IGF-1, both of which stimulate mitogenic and antiapoptotic pathways (Pollak 2008; Ramasubbu and Rajeswari 2023)<br>These conditions create a protumorigenic environment by enhancing glucose uptake in cancer cells, promoting angiogenesis, and reducing apoptosis | High red and processed red meat intake is positively associated with the risk of type 2 diabetes mellitus (T2DM; Pan et al. 2011) and correlates with biomarkers of IR (Fretts et al. 2015; Zelber-Sagi et al. 2018)<br>Diets high in glycemic load and processed/ red meat exacerbate insulin resistance, with elevated IGF-1 levels independently linked to increased risks of colorectal, breast, and prostate cancers (Giovannucci 2001; Venkateswaran et al. 2007; Endogenous Hormones and Breast Cancer Collaborative Group 2010; Rinaldi et al. 2010), among others | Proposed mechanism is indirect and not specific to red meat; associations may reflect overall energy balance rather than meat-specific effects<br>Moderate consumption of lean, unprocessed red meat—especially when replacing refined carbohydrates—does not consistently impair insulin sensitivity and may even improve short-term glycemic control<br>For other cancer sites, prospective studies on IGF-1 axis components have been inconclusive (e.g., null associations in pancreatic cancer; Douglas et al. 2010; Rohrmann et al. 2012), whereas lower IGF-1 levels were associated with higher hepatocellular carcinoma risk (Lukanova et al. 2014) |
| **Xenosialitis: Neu5Gc xeno-autoantigen and anti-Neu5Gc antibodies** | Dietary Neu5Gc from red meat is metabolically incorporated into epithelial and endothelial tissues throughout the body<br>The foreign xeno-autoantigen interacts with preexisting circulating anti-Neu5Gc antibodies, potentiating low-grade, chronic inflammation<br>This appears to be a pathogenic process largely specific to humans | The only proposed mechanism unique to red meat due to abundant Neu5Gc in commonly eaten mammalian tissues<br>Human red meat-associated cancer risk appears to be species-specific<br>Enhances chronic inflammation and carcinoma growth in animal models<br>Glycan microarrays allow high-throughput profiling of serum antiglycan antibodies, helping identify potential biomarkers and immune responses to dietary Neu5Gc (Marglous et al. 2024) | Human studies linking anti-Neu5Gc antibodies and red meat to cancer risk are not conclusive<br>Mechanistic details, such as GI uptake, selective incorporation into tissues, and total body burden of Neu5Gc, require further study<br>Cancer-specific generation of Neu5Gc under hypoxic conditions has been suggested (Bousquet et al. 2018) but remains unproven |
| **Bovine meat and milk factors (BMMFs)** | Virus-like circular DNA elements (BMMFs) present in beef and dairy may contribute to colon and breast cancer risk (Bund et al. 2021; de Villiers and Hausen 2021)<br>Early life latent infection may induce immune tolerance; persistent BMMFs could trigger chronic inflammation that promotes tumorigenesis | Epidemiological correlations between high beef/ dairy intake and increased cancer risk<br>Consistent with the inflammation-cancer paradigm<br>Suggested overlap with Neu5Gc-induced xenosialitis | Proposed mechanism is limited to beef/dairy from cattle, not all red meats<br>Remains speculative and highly controversial<br>BMMFs not universally recognized as infectious agents; direct causal evidence lacking |

Gerba and Smith 2005). In the United States, this polluted runoff is largely exempt from regulation under the Clean Water Act, as it is legally categorized as a "nonpoint source pollutant" (Olmstead 2010). Unlike *all* human waste, which is treated with bacterial, chemical, and mechanical filtration before being released into the environment, animal waste stored in man-made ponds is not treated before being applied for agricultural purposes, so when animal waste escapes from its original point source, the elevated nutrient levels of nitrogen and phosphorus contained within runoff leads to eutrophication in the surrounding surface waterbodies (Hallegraeff 1993; Mallin 1994; Glasgow et al. 1995; Hooda et al. 2000; Weldon and Hornbuckle 2006). Agriculture is responsible for 78% of global ocean and freshwater eutrophication and remains one of the major causes of significant alterations in biodiversity and ongoing water contamination throughout the world (Hooda et al. 2000; Hu et al. 2017; Poore and Nemecek 2018).

In short, global red meat production and consumption poses immediate threats to the Earth's biosphere and its inhabitants, yet the full extent of its impact remains largely unknown. Although modern advances in postindustrialized nations have greatly decreased the price of meat, the recent global economic downturn has somewhat reversed this in many low-income nations, where the price of meat remains relatively high. It is likely that the rising prices, costs (both direct and indirect), and shrinking environmental resources will form the biggest bottleneck in the growth of global red meat consumption throughout the 21st century. This may be the first financial sign of the unsustainability of red meat production. However, with the world's population now above 8 billion people and the many expanding economies, there will be a continued push for larger-scale industrial farming operations to meet the growing demand of meat consumption. This unprecedented scale of animal production in the history of *Homo* will amplify the risk of new zoonotic infections and spread of disease and result in further biodiversity loss, deforestation, antimicrobial resistance, pollution, environmental injustice, and associated health disparities (Driscoll 2022). At present, industrial agriculture carries substantial risks to both human and environmental health, with the most monumental threat emanating from the practice of intensive livestock production, also referred to as concentrated or confined animal feeding operations (CAFOs).

## Increase of Zoonotic Diseases and Rise of Antibiotic Resistance

Most animals are reared on factory or industrial farms known as CAFOs in the United States, with more than 100 million land animals raised for slaughter annually—their meat also contributing to food waste: one-third of all purchased food is ultimately thrown into landfills (Yu and Jaenicke 2020; U.S. Department of Agriculture undated). As the name suggests, CAFOs concentrate all kinds of livestock into tight quarters—quarters that provide little room to move, let alone to behave or socialize normally—to maximize production. As a result of these intense rearing practices, there are now serious risks that threaten livestock, human, and planetary health (Hollenbeck 2016). Raising tens of thousands of animals in cramped conditions for human consumption is a principal incubator for the previously mentioned *zoonotic diseases*, infectious conditions caused by bacteria, viruses, parasites, and fungi that spread between animals (typically vertebrates) and humans (Hundal et al. 2016; Conrad et al. 2017; Delabouglise et al. 2017; Bernstein and Dutkiewicz 2021). Such intensive animal rearing is a primary driver of significant land-use change that results in biodiversity loss and replacement of natural biodiversity with a dense population of a single species exhibiting low genetic diversity (Espinosa et al. 2020; Bernstein and Dutkiewicz 2021). Declines in biodiversity heighten the risk of pathogen spillover: farm animal population size and density increase, along with their high genetic similarity, thereby easing the transmission and mutation of pathogens in a veritable livestock playground (Rohr et al. 2019). At the same time, the conversion of natural habitats into agricultural

land fosters greater interactions among humans, domesticated animals, and wild animals, further elevating the risk of pathogen spillover (Rohr et al. 2019).

The concentration of susceptible animals results in unequaled environmental contamination with pathogens, fostering the development of highly transmissible and virulent pathogens. Over 700 human pathogens have been identified as zoonotic (Woolhouse and Gowtage-Sequeria 2005) and around 75% of emerging infectious diseases originate from zoonotic sources, with most of these pathogens having been directly associated with environmental changes and the expansion of CAFOs (Espinosa et al. 2020; Bernstein and Dutkiewicz 2021). CAFOs are intimately linked to the emergence of hypertransmissible avian influenza viruses, hepatitis E virus, *E. coli* O157:H7, *Streptococcus suis*, livestock-associated methicillin-resistant *Staphylococcus aureus*, and *Cryptosporidium parvum* in agricultural animals (Guo et al. 2021). Increased transmission of zoonotic pathogens to humans is a major concern at these large production facilities, leading to drastic changes in human disease patterns within local communities. This is evidenced by frequent disease outbreaks through both direct and indirect contact with farm animals (as well as the widespread presence of similar serotypes or subtypes in both humans and farm animals in high-income countries; Guo et al. 2021). The emergence and spread of these community-acquired infections are influenced by sociocultural habits and socioeconomic status (Weber and Rutala 1999; Umar and Nura 2008; Seimenis 2012). This is the reason behind such intensive and widespread livestock pharmaceutical application today (Gelband et al. 2015; Balzer et al. 2016; Van et al. 2020; Arsène et al. 2022).

Administration of antibiotics to livestock, through their feed, has a trifold purpose: prevent disease, treat disease, and enhance growth rate at so-called "subtherapeutic levels" (Manyi-Loh et al. 2018). This practice is expected to see a substantial rise worldwide throughout the 2020s, with a 67% increase in the use of antimicrobials from 2010 to 2030 anticipated (Van Boeckel et al. 2015). In 2011, roughly 80% of all antibiotics sold in the United States were used in animal agriculture, with 70% of these falling under the category of "medically important" antibiotics, e.g., those essential for human medicine. Since its peak sales year in 2015, however, there has been a notable decline this decade of approximately 38% in the domestic sale and distribution of medically important antimicrobial drugs approved for use in livestock (U.S. Food and Drug Administration 2022). Although this reported decline in 2020 indicates that ongoing endeavors to promote the prudent and responsible use of antimicrobials in these animals are trending in a promising direction, the administration of antibiotics in the costly production of cattle and hogs remains highly prevalent (Patel et al. 2020). The present and universal utilization of subtherapeutic antibiotics in red meat-producing CAFOs directly contributes to the increase of bacteria-harboring resistant genes within the intestines of animals (Looft et al. 2012). This threat is further compounded by the horizontal transfer of resistance-conferring plasmids from agricultural pathogens to human pathogens, facilitating the spread of antimicrobial resistance across distinct microbial populations (Heuer et al. 2011; Wang et al. 2023b). As a result, the emergence of antibiotic-resistant bacteria in humans becomes increasingly likely (Martin et al. 2015; Manyi-Loh et al. 2018; Patel et al. 2020). Even when used with extreme caution, antibiotics invariably contribute to resistance over time. In fact, just living near high-density red meat production is associated with exposure to methicillin-resistant *S. aureus* strains (Klein et al. 2007), a growing public health concern for over half a century (Barber 1961; Lowy 1998; Ito et al. 2001; Graffunder and Venezia 2002; O'Shaughnessy et al. 2009; Donham 2010) that has also historically disproportionately affected low-income and minority communities (Wing et al. 2000; Edwards and Ladd 2001; Wing 2002). Yet another ironic phenomenon of red meat production in human evolution is the sad reality that, in the United States, those who live within the vicinity of these massive, multithousand-head facilities live in food deserts with limited availability of locally grown fruits and vegetables and

an abundance of processed and packaged foods (Figure 5).

Farming today is characterized by marked consolidation of control and ownership of animal production, having forced small farmers out of business and permanently altering local communities and global economies. The subsequent and unavoidable rise in life-threatening infections, endangering the tried-and-true effectiveness of antibiotics that have historically worked to suppress them, has now become one of the top global public health threats (Ventola 2015). The widespread administration of antibiotics in animal agriculture and beyond has resulted in cumulative "antibiotic pollution," where the half-life of antibiotics varies from hours to hundreds of days—with residues that persist far beyond that time frame (Samreen et al. 2021). Found predominately in animal waste, many of these residues contaminate the environment and ultimately give rise to new antibiotic-resistant microorganisms (Samreen et al. 2021).

## Conclusion: From a Blessing to a Curse

Animal-derived foods, including mammalian skeletal muscle (aka "red meat") and its associated contents, were likely important components of early hominin diets and continue to influence food practices worldwide. Yet the nature, scale, and context of red meat consumption today differ drastically from those of our evolutionary past. In both high-income and rapidly developing societies, the industrial overproduction and overconsumption of red meat now contribute to multiple, well-documented global challenges: rising rates of chronic disease, environmental degradation, climate disruption, and widening social inequities—all within a global population

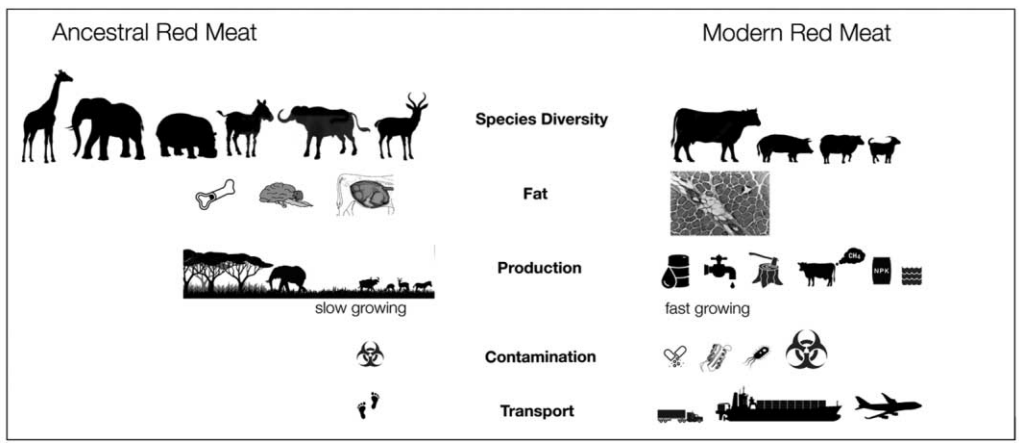


Figure 5. Contrast Between Ancestral and Modern Red Meat

During much of human evolution, only wild meat was consumed until the introduction of animal domestication in the last 12,000 years. Many more different species of animals were consumed, most of which had mostly lean muscle meat. Most fat came from bone marrow, brain, and viscera, in contrast to the intramuscular marbling and thick subcutaneous fat in modern red meat from grain fed animals. Contemporary red meat production for the global market is highly resource-intensive, requiring substantial fossil fuel inputs, water, and land, thereby driving deforestation for pasture. Ruminant livestock contribute substantially to methane emissions, while fertilizer use and animal waste often contaminate waterways. Chronic antibiotic use in livestock selects for resistant bacterial pathogens, and the final product maybe adulterated with antibiotics and growth hormones while also harboring emergent biological contaminants—including prions, microbial pathogens, and helminths—whose prevalence is amplified under intensive CAFO production systems (e.g., influenza A virus and pathogenic *E. coli* strains). The long-distance transport of red meat in refrigerated containers by land, sea, and air further contirbutes to a substantial ecological footprint.

that is approaching 9 billion. Addressing these issues requires situating red meat within a broad comparative and historical framework that acknowledges both its evolutionary significance and the health, planetary, and societal consequences of its modern patterns of production and consumption. While earlier dietary guidance recommended limiting red meat intake (Willett et al. 2019), the current Dietary Guidelines for Americans (2025–2030) recommend increased protein consumption—nearly doubling intake for the average person—with greater reliance on animal-source foods (Mozaffarian 2026). This shift contrasts sharply with decades of evidence linking higher intakes of saturated fat and red meat to increased risk of heart disease, diabetes, and cancer (Fraser 1999; Key et al. 1999; Singh et al. 2003; Bleich et al. 2026; Giosuè et al. 2026). The current guidelines also omit recommendations to limit processed red meat consumption, despite its established association with chronic disease today.

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