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Evolution of human diet and microbiome-driven disease

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During hominin history, innovations such as cooking have made a wider selection of dietary sources of energy accessible. In recent times, cooking has moved from the home kitchen to the factory with the diet of many people dominated by commercially prepared foods that are often high in fat and low in fiber content. Cooking has also introduced a variety of flavoring spices and herbs into our diet that have intrinsic anti-microbial properties. In this review, we will focus on a changing diet's effects on the gut microbiota with particular emphasis on the availability of dietary fiber as a fermentable substrate for the gut microbiota. The connection between the amount of fiber in our diet and chronic inflammation has been long known. Is the link between low fiber intake and inflammation a direct effect resulting from eating more 'inflammatory food' or an indirect effect via a diet-induced unhealthy change in the microbiome? Understanding the explanation for food-related inflammation is critical to our ability to develop novel strategies to treat the modern epidemic of obesity and inflammatory diseases.

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Introduction

Foods with low nutrient content are often referred to as empty calories, but these 'junk foods' may have negative effects on health primarily because of their impact on gut microbial ecology [1]. Recent work has shown that changes in the microbiota are central in the initiation of chronic inflammatory diseases, including autoimmune, metabolic and cardiovascular diseases [2]. A diverse microbiota is important for the maintenance of gut and host health [3,4]. As gut microbes preferentially feed on dietary fibers as their substrate for fermentation, a high fiber diet may be the proper match for maintaining a gut microbiome needed for the health of the human host. Conversely, a low fiber diet may be considered 'mismatched' for the needs of both the host and its gut microbiome. The modern industrialized diet, high in ultra-processed foods, can provoke changes in the function and diversity of the microbiome that increase the risk of developing chronic inflammatory diseases [5]. Certain easy-to-digest energetic substrates such as simple sugars were absent from the diet during most of hominin evolutionary history. On the other hand, modern diets rich in processed foods also are relatively deficient in fiber. These mismatches may have a previously unappreciated role in the progression of modern epidemics of obesity and systemic inflammatory diseases.

Cooking – a processed food innovation that makes us human

Although processed food has a role in contributing to chronic diseases, it is important to recognize that food processing began with cooking approximately 250 thousand years ago and has been cited as a key adaptation in human evolution [6]. One major benefit of cooking is the reduction in food borne infection, a ubiquitous risk during human evolution [6]. Processing meats and vegetables by cooking has been proposed to also increase the availability of food energy in the diet [7•,8,9], (Table 1). Cooking has been reported to increase the digestibility of starch by 35–40% facilitating the absorption of the end products of carbohydrate digestion [13]. By increasing the availability of easily absorbed carbohydrates for rapid assimilation, successful capturing of food energy becomes less dependent on bacterial fermentation in the large bowel [7•]. As a consequence, humans have a much smaller length and mass of the bowel compared to primates with a larger overall body size, such as gorillas. The enhanced digestibility of nutrients entering the gut after food processing and cooking may mean that more dietary energy can be exploited by both vertebrate host and those members of the microbiota that do not rely on fermentation of poorly digestible starches including fibers [14]. Carmody *et al.* recently showed that cooked tuber, as compared to raw tuber, resulted in increased body mass in mice and produced a distinct community structure of the intestinal microbiome in both mice and humans [11••]. Notably, raw tuber contained defensive secondary plant compounds

Table 1

Increased energy from cooking

Food	Effect of cooking	Proposed mechanism	Reference
1. Oats	12.1% ↑ energy availability (ileal digestibility)		
2. Wheat	14.5% ↑ energy (ileal digestibility)	Gelatinization and hydrolysis of starch	[10]
3. Plantain	30.2% ↑ energy (ileal digestibility)		
4. Tuber	↑ body mass in mice	Gelatinization and hydrolysis of starch	[11••]
5. Egg protein	45–78% ↑ energy (ileal digestibility)	Protein denaturization	[12]
6. Meat	↑ weight gain in mice	Collagen gelatinization. Reduced pathogens and immune expenditure	[7•]

that exerted an antimicrobial effect on gut microbes, as measured by reduction in bacterial load and evidence of microbial cell damage, that was comparable to that of the antibiotic ampicillin [11••]. The antimicrobial effect was absent with the cooked tuber or standard chow. A variety of *in vitro* studies have suggested that raw fruits and vegetables have higher levels of phenolics and flavonoids that exert antimicrobial and anti-inflammatory effects as compared to their cooked counterparts [15]. For example, the phenolic compound coumaric acid in chile peppers and orange peels is responsible for the antimicrobial effects in those foods [16]. With cooking, flavorful herbs and spices became important components of many cuisines. Many spices and herbs have antimicrobial properties exerted by compounds such as cinnamic aldehyde found in cinnamon and carvacrol and thymol found in oregano [17]. The overall effect of cooking on the antimicrobial properties of spices and herbs is mixed. For example, there is no impact on the antimicrobial effects of cooked oregano. On the other hand, cooking in extra virgin olive oil can enhance the availability of antimicrobial phytochemicals, such as tomato lycopenes [18,19].

Besides altering the anti-inflammatory and antimicrobial properties of various plant foods, cooking generates pro-inflammatory advanced glycation end products (AGE). Dietary AGE elicit inflammatory signalling by interacting with transmembrane receptors (RAGE) found on a wide variety of cells, including macrophages. AGE may also adversely affect the microbiome. These molecules have been shown to reduce both alpha diversity and fiber fermenting microbes, such as *Alloprevotella*, while boosting the numbers of potentially harmful *Desulfovibrio* and increasing permeability of the rat intestine [20].

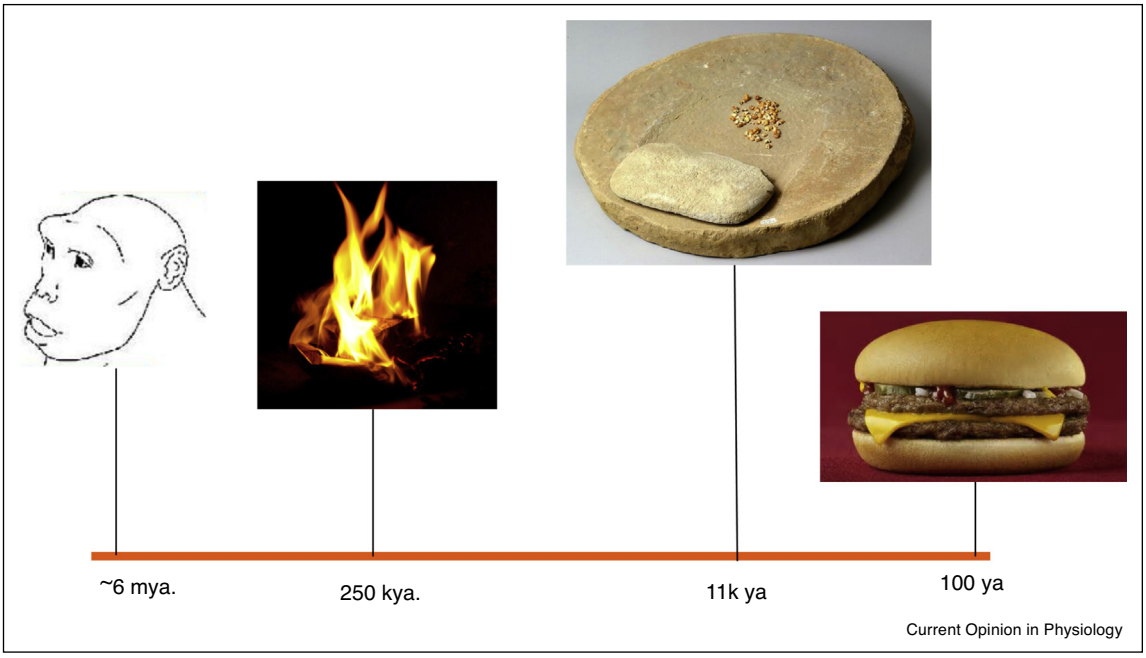
Lower fiber

Besides cooking, human food processing in traditional societies includes the reduction of dietary fiber by pounding and grinding of plant foods and dehulling of grains [21,22•,23] (Figure 1). Chimpanzees, the ape with which humans most recently shared a common ancestor, about 6 million years ago, consume a diet high in raw fruit that is far greater in plant fiber compared to the diet of most humans [24]. More distantly related great apes, including orangutans and gorillas, are foliovores, with a diet that consists mainly of leaves. Obtaining this energy necessitates dependence on fermentation by fibrolytic microbiota (microorganisms that process complex plant polysaccharides due the availability of cellulotytic and hemicellulolytic digesting enzymes) in the cecum, which is comparatively larger by mass compared to that of humans. Humans derive approximately 10% of dietary energy from fiber fermentation to short chain fatty acids, compared to approximately 60% in gorillas [25]. *Australopithecus*, an early hominin genus that existed in the late Pliocene era 2 million years ago, also had a larger colon, smaller proximal gut, and larger gut overall compared to modern human, suggesting a greater reliance on dietary fiber. Some modern humans following a traditional lifestyle, including the Hadza of Tanzania and Tsimane of Bolivia, consume consume diets relatively higher in fiber when compared to diets typical in the industrialized world [26•]. The microbiota of humans eating industrially processed foods exhibit marked changes as compared to that of humans on a traditional high-fiber diet [27•] and the microbiomes of wild apes [28]. It is important to recognize that key food components including fiber, do not have uniform effects on the microbiome across various primate species. The microbiomes of multiple primate species have been shown to respond differently to changes induced by a low fiber 'Western'-style diet [28].

The Western diet – industrially processed and fiber deficient

Although longstanding evolutionary trends in hominin lineages have favored the reduction in fiber and increase in energy density and energy availability, modern industrialized food preparation has taken food processing to an unprecedented level. The Western diet is defined as being high in simple carbohydrates, saturated fats, sugars, and has low levels of fruit and fiber. The connection between the amount of fiber in the diet and chronic inflammation was highlighted in the 1970s by Thornton *et al.* when the authors found that the diet of Crohn's patients was low in fiber before they became ill [29]. In a follow up uncontrolled trial, Heaton *et al.* provided further support for the idea that diets low in fiber are inflammatory by showing that a high-fiber diet protected Crohn's

Figure 1



Key events in the evolution of hominin diet. The common ancestor of chimpanzees and humans existed approximately 6 million years ago. Cooking coincides with the appearance of *Homo sapiens* 250 thousand years ago. Agriculture appeared approximately 11 000 years ago along with the processing of grains (metate and ancient maize in this image). Modern industrial food processing appeared in the first half of the last century.

patients from hospital admission when compared to a diet high in refined sugars [30]. Dietary fiber has been associated with improved outcomes in a variety of gastrointestinal diseases (Table 2). The health protective effects of dietary fiber include the maintenance of the mucin barrier [35•], inhibition of pathogenic bacterial intestinal adhesion and translocation [36], decreased pH via short chain fatty acid production [37], and competitive exlusion of pathogens by fiber fermenting microbes [38]. In addition, dietary fiber maintains a diverse microbial ecosystem in the gut [26•,39] that prevent overgrowth of harmful species,such as *Clostridiales difficile* [40].

Western diet has been linked to unfavorable changes of the microbiota and impaired mucosal barrier leading to microbial translocation, leading to downstream intestinal and systemic inflammation [35•,41]. Blooms of harmful pathobionts (opportunistic pathogens) are reported with the Western diet [42]. Increasing fiber in the diet tends to have the opposite effect. Even short term changes in the diet can affect bacterial translocation and barrier function. Seven days of oral feeding with total parenteral (TPN) solution as fiber-free food resulted in bacterial translocation in 60% of rats when compared 0% of rats fed normally. The addition of fiber in the form of cellulose

Table 2

Fiber and the risk of gastrointestinal diseases

Diet	Disease	Effect	Design	Reference
Dietary fiber	Crohn's disease	↓ risk	Observational	[29]
High fiber diet	Crohn's disease	↓ risk	Observational	[31]
Fiber supplemented diet	Crohn's disease	Mixed clinical effects ↓ inflammatory biomarkers	Systematic review of randomized controlled trials	[32]
Fiber supplemented diet	Ulcerative colitis	↓ disease activity	Systematic review of randomized controlled trials	[32]
Mediterranean diet (high fiber)	Non-alcoholic fatty liver disease	↓ steatosis ↑ insulin sensitivity	Randomized controlled trial	[33]
Dietary fiber	Non-alcoholic fatty liver disease	↓ risk	Observational trial, multiethnic population	[34]

reduced bacterial translocation in the oral TPN-fed group to 8% [36]. The beneficial effects of dietary fiber in preventing bacterial translocation may be achieved relatively easily. In the oral-TPN-fed rats, 2.5 g of cellulose per day for 7 days was sufficient [36]. In humans, the addition of orange juice has been shown to prevent endotoxemia and inflammation after an energy dense meal, perhaps because of its fiber and flavonoid content [43].

Dysbiosis, barrier impairment and obesity

Although obesity has been linked to changes in the microbiota, uncertainty persists about the causal links between microbiota and the obese phenotype. One hypothesis is that obesity results from increased energy harvest by fermentation of indigestible carbohydrates in the distal gut [44]. This hypothesis was originally formulated based on lower weight gain observed in gnotobiotic mice relative to conventionally raised animals [3]. Non-digestible carbohydrates are converted by colonic fermenters to produce short-chain fatty acids, including acetate, propionate, and butyrate. Short chain fatty acid (SCFA) absorption in the colon is estimated to provide between 5–10% of daily energy requirements in humans [25]. SCFAs are detectable in feces, and elevated levels, suggestive of heightened energy extraction, were found in obese subjects [45,46]. In particular, the increased ratio of two bacterial phyla, Firmicutes and Bacteroidetes, has been argued to be responsible for increased energy extraction capacity [47]. An altered Firmicutes/Bacteroidetes ratio in obesity was also reported in some human studies [48–50], although other studies failed to find this relationship [46,51]. While the described shift in Firmicutes and Bacteroidetes was also reported for obese mice in a later study, no clear relationship between energy extraction capacity and gut microbiota phyla was found [52].

Microbial genes for fiber fermentation have been shown to be increased in the obese state, but fiber-supplemented diets have complex effects on energy metabolism [53]. Complex carbohydrate intake increases short chain fatty acids, but also has been shown to increase satiety and reduce weight gain in animal models and in humans [54]. In mice, dietary supplementation with butyrate had protective effects against dietary-induced obesity [55]. These findings cast doubt on the hypothesis that fiber digestion is the central cause of obesity.

A second hypothesis, termed metabolic endotoxemia, points to translocation of lipopolysaccharide (LPS) and bacteria as a source of visceral adiposity and inflammation [41]. A 'Western-style' diet, rich in sugar and fat, is associated with inflammation and dysbiosis, such as bacterial blooms in *Mollicutes* and a reduction in species richness in both Bacteroidetes and Firmicutes in mice [44].

Dysbiosis caused by high fat diets is extensively documented in animal models [42,56–58] and is a probable cause of diet-related LPS entry into blood (postprandial endotoxemia) [43,59] and obesity [60,61]. Several studies have implicated bacterial and LPS translocation in inflammation and weight gain associated with a diet high in fat and simple carbohydrates [60,62]. Lending further support for this hypothesis, antibiotic administration was found to prevent diet-induced inflammation and obesity [41].

Notably, saturated fats and omega-6 polyunsaturated fatty acids (PUFA) are more likely than other fats (e.g. omega-3 PUFA) to cause dysbiosis. These same fats are linked with the development of chronic inflammatory diseases [63]. Dysbiosis from a high-fat diet is accompanied by increased intestinal epithelial cell adhesion of pathobionts and pathogens and translocation of bacteria and LPS into the circulation, reviewed in Ref. [64]. By interfering with host barrier function and promoting metabolic endotoxemia, a high fat diet might predispose to obesity.

In addition to their obesogeneic effects, dietary simple sugars, such as fructose, increase the risk for non-alcoholic steatohepatitis (NASH) [65], in part by causing lipogenesis by metabolism of fructose and intrahepatic accumulation of lipids [65]. Small intestinal bacterial overgrowth (SIBO) and NASH often co-occur and share a common pathophysiologic pathway involving exposure to lipopolysaccharide [66]. Increased bacterial load in the small intestine, as occurs in subjects with SIBO, increases intestinal permeability and results in translocation of bacteria and LPS [67], reviewed in Ref. [68]. The small intestine is thinner-walled, and it imposes a less robust barrier to microbial translocation as compared to the colon.

Fiber intake and dominance of fibrolytic versus mucinolytic microbes

A great deal of knowledge on the effect of dietary fiber on gut microbes has come from work exploring the response of *Bacteroides thetaiotaomicron*, a carbohydrate-foraging resident gut microbe to a change in the availability of dietary fiber. On a high fiber diet when the energy source of gut microbes come from exogenous fermentable carbohydrates, *B. thetaiotaomicron* was found to have upregulated expression of genes needed for breaking down fibers such as those related to glycoside hydrolases including xylanases, pectate lyase and arabinosides. However, on a low fiber diet, a switch in gene expression took place with increased expression of a different set of glycoside hydrolases along with enzymes involved in harvesting glycans from host mucin as the endogenous source of fermentable substrates such as sialidase, sialic acid-specific-9-*O*-acetylesterases, mannosidase and three β-hexosaminidases [69]. *B. thetaiotaomicron* also expresses

genes for α-fucosidase allowing this bacteria to harvest fucose from host mucin glycan [70]. The availability of exogenous fiber may also determine the composition of the microbial community as a number of gut microbes have been found to have mucin-degrading ability such as *Ruminococcus torques* and *Ruminococcus gnavus* belonging to *Lachnospiraceae* family in the phylum Firmicutes [71,72]. Mucin-foraging capability has also been found in members of the phyla Bacteroidetes, Actinobacteria, and Verrucomicrobia. *Akkermansia muciniphilia*, a member of Verrucomicrobia, is one of the best characterized and most commonly found mucin-degrading bacteria in healthy individuals. This microbe is capable of extracting carbon and nitrogen entirely from mucin [73]. The gut microbiota in inflammatory bowel disease (IBD) contains a greater number of mucin-degrading bacteria [74] but, surprisingly patients with IBD have fewer of *A. muciniphilia*, Similarly, *Faecalibacterium prausnitzii*, another common mucin-degrading mucosa-associated bacteria was reduced in number in patients with Crohn's disease [75], a finding related with greater numbers of aggregative, adherent *Escherichia coli* [76]. In some circumstances, carbohydrate provisioning to microbes by the host in the form of mucin production or fucose secretion can encourage a host–microbiome mutualism [1,77]. Some mucin-degrading bacteria such as *A. muciniphila* are anti-inflammatory and appears to be protective against inflammatory conditions such as IBD [74] and Type 1 diabetes mellitus [78] and Type 2 diabetes mellitus [79] in part because of strengthening of gut barrier function. Other mucin-degrading bacteria such as *R. torques* appear to be harmful by breaking down the protective barrier formed by intestinal mucin to allow translocation of bacteria and bacterial antigens resulting in the triggering of unwanted proinflammatory response by the host [80]. Available information would then suggest that a low fiber diet might favor mucinolytic bacteria over fibrolytic bacteria with downstream adverse effects such as loss of protective barrier, microbial translocation and a pro-inflammatory response. However, exceptions exist such as the sometime beneficial effects of *A. muciniphila* [81].

The mucus layer, produced by goblet cells in the intestinal epithelium, has a barrier function that reduces bacterial translocation and prevents inflammation and certain enteric diseases. Recent work suggests that consumption of a Western diet causes an overgrowth of mucus grazing bacteria that can weaken the intestinal barrier, potentially increasing the risk for obesity and diabetes [35•]. In addition, a thick mucin barrier provides habitat for protective bacteriophage that reduce the number of bacteria migrating through the mucin barrier and antagonize bacterial aggregation and adhesion at the intestinal epithelium [82]. Furthermore, this mucin plays an essential role in the bacteriophage–bacteria interaction that works to regulate the microbial populations in the luminal space [83•,84,85].

Antimicrobial foods and chronic low-grade inflammation

Wasielewski *et al.* made the counterintuitive suggestion that foods that are more difficult for the host to process should be associated with better health in modern humans (compared to easy-to-process substrates that lead to competition between host and resident microbes) [1]. It is already widely appreciated that healthy diets, resulting in healthy microbiota and a healthy immune system, are characterized by the presence of foods that counteract the growth of pathobionts and pathogens. However, a healthy diet is one that promotes the growth of a complex and diverse microbial ecosystem that is resilient to disturbances and can reduce the likelihood of infection [86].

Paradoxically, health-promoting nutrients are generally foods with antimicrobial properties; these inhibit the growth of pathogens and pathobionts. Antimicrobial nutrients include omega-3 fatty acids, sialylated oligosaccharides, and polyphenols in fruits and berries [87]. Dietary fiber serves as a fermentation substrate for short chain fatty acids that are anti-inflammatory and also reduce the intestinal pH, thus protecting against pathogen overgrowth and infection [64]. Many fermented foods have a low pH because of lactic acid and tend to have anti-pathogen and anti-inflammatory properties [88]. Cooking in most cases reduces the anti-microbial activity of foods, particularly in plants, reviewed in Ref. [19]. Speculatively, the relative increase in inflammatory potential from cooked food versus raw vegetable foods is a price that early and modern humans are willing to accept in exchange for the higher energy that can be derived from cooked food. From an evolutionary perspective, human physiology has evolved in the context of that tradeoff to take advantage of the energy benefits from a minimally processed (cooked) diet. The absence of antimicrobial activity in certain cooked foods may be mitigated by the very low gastric juice pH seen in humans (pH 1.5) relative to other primates [89]. The addition of antimicrobial spices to foods might similarly restrain the growth of harmful microbes in some cases [18].

Avoiding industrially processed foods

It has been argued that modern humans seek out industrially processed foods for the same reasons our ancestors prioritized cooked foods and minimized the effort needed to acquire dietary energy. Obtaining calorie dense foods with easily accessible energy likely resulted in a fitness payoff for ancestral humans [90,91]. The argument for cooked food follows the same logic [7•]. However, our modern industrialized environment is characterized by the unlimited 24-hour availability of low-fiber ultra-processed calorie-dense foods. Whereas pre-modern humans and modern humans living a traditional lifestyle have co-evolved with cooked food and a microbiota shaped by that diet, the consequences of an ultra-processed diet are evolutionarily new. The loss of dietary fiber in ultra-processed diets may shift the microbial community from

fibrolytic bacteria to mucinolytic bacteria. A potential consequence of this shift is a reduced protective mucin layer leading to translocation of bacteria and/or bacterial antigens with a proinflammatory host response and increased risk for chronic inflammatory diseases. Human adaptations, including the low pH of the proximal gut, along with cultural innovations such as the use of spices in food [91], might mitigate against the inflammatory burden that comes with cooking. However, contemporary humans are not equipped to chronically ingest diets with unlimited refined carbohydrates and absent dietary fiber. In these ways, modernity has outpaced longstanding evolutionary trends. In particular, modern diets and lifestyles have accelerated dietary inflammation linked with chronic diseases. This is not to say that we can or should adopt a stone age diet as proposed by others [92]. Instead, we need to understand that a tradeoff exists between energy availability in food and the inflammation generated by the microbiome. We have evolved to negotiate that tradeoff successfully throughout human evolution, but modern industrialized food has unbalanced this tradeoff in a way that is inconsistent with long term health.

Conflict of interest statement

Nothing declared.

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