Lipids in Health and Disease

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Saturated fat in an evolutionary context

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Abstract

Evolutionary perspectives have yielded profound insights in health and medical sciences. A fundamental recognition is that modern diet and lifestyle practices are mismatched with the human physiological constitution, shaped over eons in response to environmental selective pressures. This Darwinian angle can help illuminate and resolve issues in nutrition, including the contentious issue of fat consumption. In the present paper, the intake of saturated fat in ancestral and contemporary dietary settings is discussed. It is shown that while saturated fatty acids have been consumed by human ancestors across time and space, they do not feature dominantly in the diets of hunter-gatherers or projected nutritional inputs of genetic accommodation. A higher intake of high-fat dairy and meat products produces a divergent fatty acid profile that can increase the risk of cardiovascular and inflammatory disease and decrease the overall satiating-, antioxidant-, and nutrient capacity of the diet. By prioritizing fiber-rich and micronutrient-dense foods, as well as items with a higher proportion of unsaturated fatty acids, and in particular the long-chain polyunsaturated omega-3 fatty acids, a nutritional profile that is better aligned with that of wild and natural diets is achieved. This would help prevent the burdening diseases of civilization, including heart disease, cancer, and neurodegenerative conditions. Saturated fat is a natural part of a balanced diet; however, caution is warranted in a food environment that differs markedly from the one to which we are adapted.

Keywords Saturated lipids, Evolutionary medicine, Nutrition, Mismatch, Evolution

Introduction

Saturated fat has incited significant controversy in the nutrition community. A longstanding notion is that a high intake of saturated fatty acids (SFAs) increases low-density lipoprotein cholesterol (LDL-C) and heart disease risk; however, this position has been challenged by studies finding no conclusive evidence of such an effect [1–4]. The discrepancy has given rise to opposing views and discussion, both in the scientific literature and popular press [5–9].

Ascertaining what constitutes an appropriate nutrient intake level is important for a number of reasons, such as setting healthful dietary guidelines, advising individuals, patients, and groups, and communicating sound nutrition advice to the public. At present, dietary guidelines commonly recommend limiting the intake of SFA-rich foods and the energy contribution from saturated fat to less than 10% of total calories [10–13]. It is the official policy in the United States, Australia, and many European nations, as well as of the World Health Organization (WHO). The controversy that has arisen over saturated fat and its role in a healthy diet propagates some doubt as to the validity of the recommendation, highlighting a need for scientific scrutiny.

Much of the work in the area has focused on investigating the physiologic effects of dietary components. While necessary, this research is limited in scope and liable to yield some inconclusive and contradictory results, due to variations in study design, methods, and samples, confounding variables, uncertainty regarding

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risk markers, and the length of time it takes for major disease to develop, among other factors. An evolutionary perspective can supplement and clarify the data derived from other methods by providing insights into the food types and nutrient intake levels that were characteristic of the human past, and hence, that are likely to be suitable for the evolved human biology.

Like other organisms, *Homo sapiens* have adapted to environmental circumstances and exposures over time, through natural selection. This Darwinian concept, central to evolutionary biology and medicine, has been invoked to explain the rise of various diseases and health disorders in contemporary societies, including, but not limited to, obesity, acne vulgaris, heart disease, cancer, and diabetes [14–20]. A mismatch between current dietary practices and those to which we are accustomed, is a core issue [14–20].

Previous scientific publications have discussed how changes in dietary FA profile have contributed to the discordance [21–24]; however, to this author's knowledge, no published paper has specifically and broadly reviewed saturated fat in an evolutionary context. In the present consideration, dietary SFA sources, yields, and effects are presented and discussed.

Considerations

Sources

Rich sources of SFAs in contemporary diets are fatty domesticated meats, high-fat dairy products, coconut oil, cocoa butter, palm oil, and highly processed foods containing one or more of these ingredients (e.g., chocolate) (Fig. 1). None of these were available to human hunter-gatherer (HG) ancestors, and hence, were not a part of the diets that exerted selective forces on the human genome over millions of years prior to the agricultural and industrial revolutions [25–27]. Of the foods that are presently consumed, meats and dairy products are major sources of SFAs.

Meats

Meats have long been a part of the human dietary constitution, with a larger contribution tracing back 2–3 million years [30–32]. Meats consumed were of the wild type, which are generally lean compared to more novel varieties sourced from domesticated animals [29, 30, 33]. Excess dietary carbohydrate from hay and grain-feed is transformed through ruminal fermentation, yielding short-chain fatty acids, and through de novo lipogenesis, yielding mostly palmitic acid (PA) (C16:0), which can be

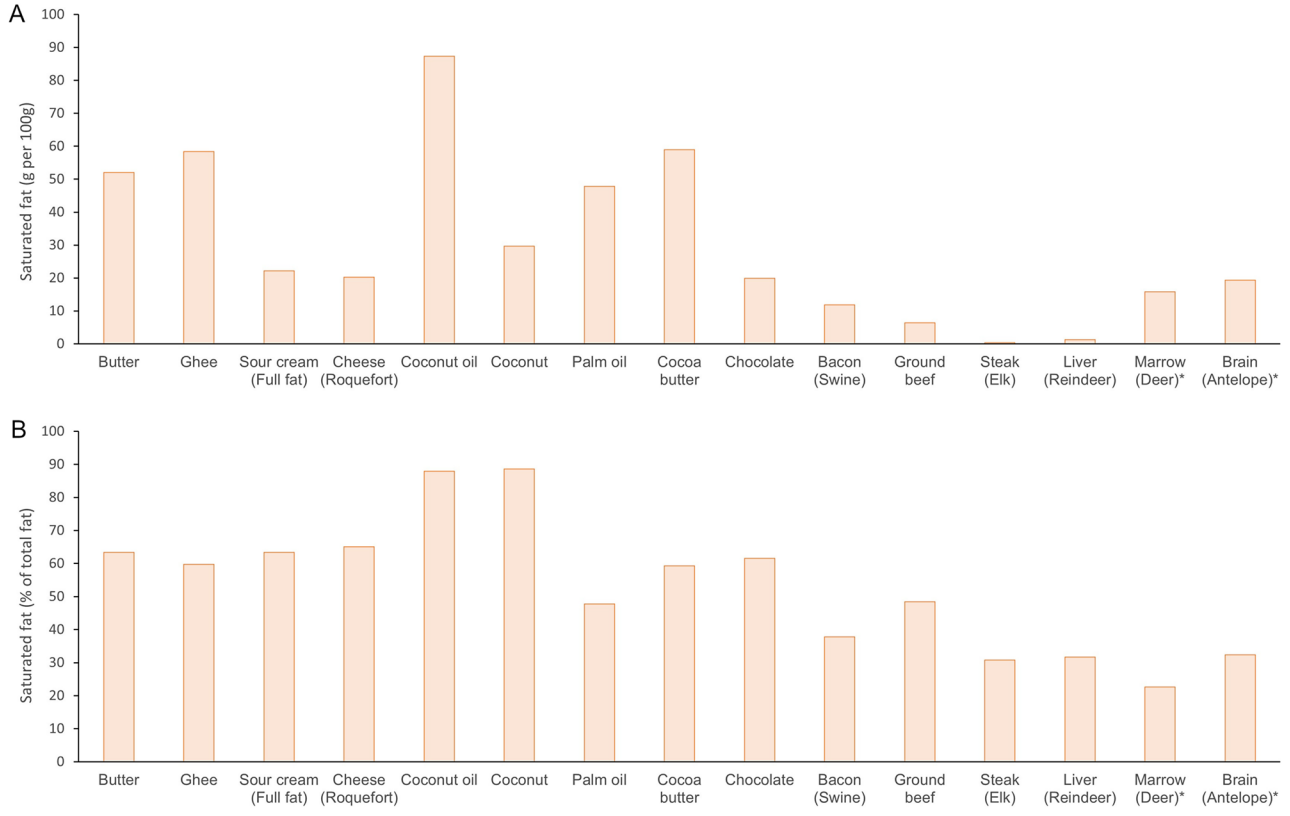

Fig. 1 Saturated fatty acids in selected foods. Values are for raw (uncooked) products. A: Grams of saturated fat per 100 g of the foods. B: Saturated fat as a percentage of the total fat content. Values for all foods are derived from official nutrient tables [28], except those of marrow and brain, which are from fatty acid analyses of wild ruminant tissues [29]. *Rear metatarsal bone marrow and homogenized brain. Fat content of the tissues vary. The values in A are based on a medium fat percentage of 70% (of total weight) in the marrow, and 60% in the brain

desaturated, elongated, or stored, promoting lipid accumulation in livestock. Wild game meat generally contains a higher proportion of unsaturated FAs (UFAs) [29, 33]. In a 2002 analysis, it was found that grain-fed beef contains 2–3 times more absolute saturated fat and 3–4 times less n-3 polyunsaturated FAs (PUFAs) than game meat [29]. In grass-fed beef, the saturated fat content is not as high, and the n-3 PUFA content is higher than in grain-fed beef, but still significantly lower than in game meat [29, 34].

In nature there is significant variation, with some wild animals depending on increased adiposity for insulation or surviving hibernation, migration, and/or food fluctuation [35]. Animal parts also vary in their fat content. Optimal foraging theory dictates that naturally living humans of the past sought to obtain the maximum number of calories for the energy they expended, implying a preference for lipid-rich sections. One such option is marrow, which was undoubtedly exploited by human ancestors and may have been a significant energy source in the ancestral human HG niche. The fatty acid composition of marrow varies between species and animals, as well as locationally within each animal, but tends to be dominated by monounsaturated FAs (MUFAs), chiefly oleic acid (OA) (C18:1), followed by SFAs mostly in the form of PA (C16:0) and stearic acid (SA) (C18:0) [29, 36–38]. The degree of unsaturation increases distally (e.g., from the proximal femur to the metatarsus), with MUFA percentages from 40 to 75% of total fat reported in different skeletal sections [29, 36–38]. Availability of fat-rich animal parts can vary across the seasons, with higher animal body fat percentages seen during foliage-rich summer and fall than late winter and spring [39], and would have depended on large game hunting and scavenging opportunities and success.

Dairy

Early evidence of dairy consumption traces back approximately 6000–7000 years [40–42]. Prior to the cultivation of livestock, humans may only have sporadically ingested the milk of other mammals, as part of hunting and eating such prey. The intake must have been limited, both due to low accessibility and digestibility. In the absence of lactase enzymatic capacity, milk consumption results in gastrointestinal distress, such as bloating and diarrhea. The severity of the symptoms depends on the amount consumed and the degree of small intestinal lactase deficiency, as well as gut microbiota composition [43, 44]. With the advent of dairy farming and availability of non-human animal milk, lactase persistence alleles increased in frequency in certain parts of the world [45, 46], allowing for more unrestrained consumption of milk and products derived from it.

Milk is a complex fluid, consisting of a variety of special growth regulators and factors (e.g., microRNAs, estrogen) [47–49], in addition to common vitamins, minerals, and macronutrients. The composition varies from species to species, as well as inter-individually, depending on genetics, diet, and other factors, and across the lactation period [47, 50, 51]. Human breast milk, consumed by the suckling infant, has mean values of 42.2% SFAs, 36.6% MUFAs, and 21.1% PUFAs across worldwide studies, with OA (C18:1) being the most abundant FA, followed by PA (C16:0), together making up ~70% of a mean total fat content of 3.40 g per 100 ml [52]. Ancestral compositions may have been somewhat similar, but affected by maternal FA profiles and intakes. Cow's milk, which is more generally and most regularly consumed by contemporary humans in western countries, consists of approximately double the amount of saturated fat relative to unsaturated fat, with PA (C16:0) being the predominant FA [53, 54]. This composition is reflected in the profile of milk-originating products such as butter, cheese, and cream [55–57].

Yields

SFA intakes vary widely across the globe, from a few percentages of the total energy intake to more than 25% [58, 59]. In the United States, saturated fat contributes on average approximately 12% of total calories, according to National Health and Nutrition Examination Survey (NHANES) data from 2017 to 2020 [60]. In almost all European countries, intake estimates exceed 10%, with means ranging from 9 to 19%, the bulk of the contribution coming from meats, dairy, and fats and oils [61, 62]. A backdrop for these values has emerged through research on evolutionary intakes.

HG intakes

In their original and seminal 1985 paper on Paleolithic nutrition, Eaton and Konner estimated that Stone Age HGs consumed more PUFAs than SFAs, with the opposite being true for the American diet, which contained more than twice as much of the latter [25]. In subsequent publications, they have updated their nutritional considerations on the basis of new data and insights, but maintain that HG FA profiles feature most of the unsaturated types, with relatively high intakes of n-3 PUFAs [26, 63, 64]. In 2010, Kuipers et al. analyzed the likely FA composition of East African Paleolithic diets with different food combinations [65]. They proposed and emphasized a greater contribution of aquatic food resources relative to terrestrial ones, raising the levels of marine fats, but also included other subsistence models in the analysis. As for the percentage of total calories derived from SFAs, estimates generally range from 6 to 12%, depending on plant/animal subsistence ratio, the types of plants and

animals consumed, and eating behavior [21, 23, 65, 66]. Assuming an energy intake of 3000 kcal/d (12552 kj/d), which may approximate anatomically modern human male HG energy requirement [67], 6 to 12 E% from saturated fat amounts to 20 to 40 g/d.

Consumption of significant amounts of meat, and in particular the most fat-rich animal parts, results in higher fat and SFA intakes relative to more plant-based menus. In a book chapter on the subject, Loren Cordain arrived at a moderately high estimate (14.5 E%) assuming a predominant energy contribution from animal source foods (55 E%), protein (26 E%), and fat (46 E%) [68]. Other authors have argued for a more prominent role of carbohydrate-rich plant foods (e.g., tubers) and honey in current and prehistoric HG diets [25, 69–71]. In addition to providing glucose for oxidation and glycogen, dietary carbohydrate would have been a potential substrate for hepatic, adipocytic, colonic, and mammary SFA generation (Fig. 2). The rate of transformation would particularly have depended on total intakes, activity level, and meal pattern. In the case of relative energy balance, but with intermittent periods of food depletion and subsequent acquisition through movement, intrinsic to self-sustaining lifeways in ancestral natural environments [72, 73], some fat could have been produced and stored in the absorptive and post-absorptive phase, and then utilized as FAs and ketones in the fasted state.

There may have been some intake differences between the sexes and/or age groups, depending on community roles, dispositions, and food procurement (e.g., hunting vs. gathering) and consumption practices. In contemporary societies and groups, a greater male than female preference for meat has frequently been reported, with women showing a comparably greater appetite for vegetable foods [78–81]. During lactation, female energy requirements are elevated, with both exogenous and endogenous FAs capable of contributing to milk lipids. Breast milk is the natural sole or majority nutrition for very small children, with a mean lactation duration per birth of 2.9 years reported in some recent and current HG groups [82]. The characteristics of these patterns in past societies would have affected intra-group and inter-individual macronutrient intakes.

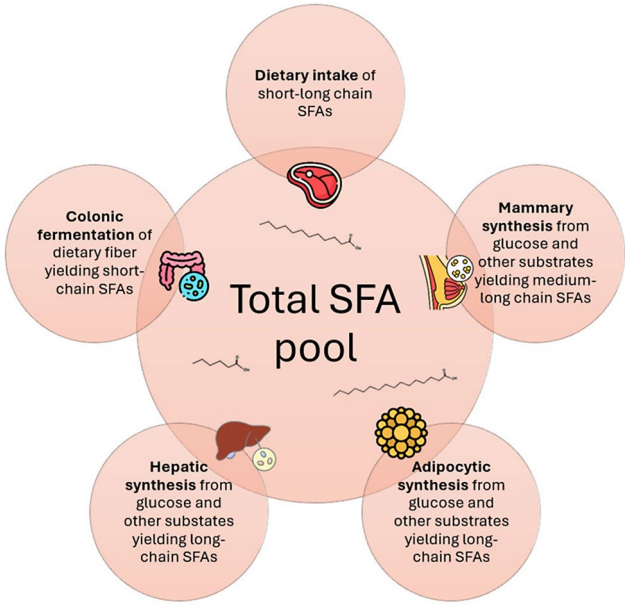

Fig. 2 Primary sources of saturated fat in the human organism. SFA = saturated fatty acid. Short-chain: ≤6 carbon. Medium-chain: >6, ≤ 12 carbon. Long-chain: >12 carbon. Information on chain-lengths is from published works on endogenous generation in different tissues [74–77]

Precise nutrient intake values are difficult to obtain for communities with a sole or predominant hunting and gathering subsistence economy, due to seasonal variation, eating out of camp, and insufficient data on wild food nutrient composition. However, inferences and rough estimates can be made from general nutritional data and knowledge. Major types of foods consumed include wild berries, fruits, roots, honey, meats, seafood, nuts, seeds, and certain legumes [25, 64, 69, 83]. These nutrient resources contain low to moderate amounts of SFAs compared to denser sources such as bacon, butter, ghee, cream, cheese, and sausages. 50 g of each of the penultimate two foods, together with 200 g of the ultimate, can singlehandedly provide upwards of 35 g of saturated fat (>10 E% on a 3000 kcal diet) [28], an intake level that is much harder to attain through the ancestral sources, in that it mostly requires vastly greater quantitative consumption. If fatty food types (e.g., marrow, brain, lipidous seafood) are sought and obtained, SFA intake will rise more rapidly than if leaner meats and vegetable foods are exclusively or mostly consumed, but due to the comparably greater concentration of UFAs than SFAs, the overall fatty acid profile will feature more MUFAs and PUFAs than if atypically SFA-rich dairy foods and meat cuts from modern domesticated animals are taken in. An example is shown in Table 1. Insects is an ancient source of nutrition that sometimes contain significant amounts of SFAs; however, they are generally not consumed in large quantities, as staple foods. Furthermore, they tend not to contain disproportionate amounts of SFAs relative to MUFAs and PUFAs. An overview is provided in Table 2.

Temporal and spatial variation

Africa features prominently in hominin history, as the birthplace of humanity and a central site of the development of archaic species (e.g., *Homo habilis*, *Homo erectus*) and early *Homo sapiens* [101]. A much-studied indigenous population is the Hadza, who occupy parts of Northern Tanzania. Their native diet consists mainly of honey, berries, fruit, meat, and tubers [83, 102]. This

Table 1 An example of animal food combinations that provide > 10% energy from saturated fat on a 3000-kcal diet

Modern foods	Amount g	SFAs g (%)	MUFAs g (%)	PUFAs g (%)	Ancestral foods	Amount g	SFAs g (%)	MUFAs g (%)	PUFAs g (%)
Sour cream (Cow)	100	22.2 (70.7)	8.4 (26.7)	0.8 (2.6)	Brain (Antelope)*	100	19.4 (39.7)	16.1 (33)	13.3 (27.3)
Yoghurt (Cow)	100	2.2 (71)	0.8 (25.8)	0.1 (3.2)	Marrow (Deer)*	100	15.8 (24)	46.1 (70)	4 (6)
Sausages (Swine and cattle)	100	6 (38)	7.6 (48.1)	2.2 (13.9)	Steak (Elk)	100	0.4 (36.4)	0.4 (36.4)	0.3 (27.2)
Minced meat (Sheep)	100	6.7 (55)	4.9 (40.1)	0.6 (4.9)	Liver (Reindeer)	100	1.3 (44.8)	0.7 (24.1)	0.9 (31)
Total	400	37.1 (59.4)	21.7 (34.7)	3.7 (5.9)	**Total**	400	36.9 (31.2)	63.3 (53.4)	18.2 (15.4)
% of 3000 kcal		11.1	6.5	1.1	% of 3000 kcal		11.1	19	5.5

SFAs = saturated fatty acids. MUFAs = monounsaturated fatty acids. PUFAs = polyunsaturated fatty acids. Values for all foods are derived from official nutrient tables [28], except those of marrow and brain, which are from fatty acid analyses of wild ruminant tissues [29]. *Rear metatarsal bone marrow and homogenized brain. Fat content of the tissues vary. The values are based on a medium fat percentage of 70% (of total weight) in the marrow, and 60% in the brain. Note that the percentage values within each fatty acid class for each food are calculated from the totaled SFA, MUFA, and PUFA contents. Other lipids that may exist in the foods are not included

Table 2 Fat content of different food types

Food	SFA content			MUFA content			PUFA content			SFA/MUFA ratio		SFA/PUFA ratio	
	Low	Medium	High	Low	Medium	High	Low	Medium	High	>1	<1	>1	<1
Dairy (including light products)													
Meats (domestic)													
Meats (wild)			Adipose tissue			Marrow			Brain tissue				
Seafood													
Eggs													
Insects													
Oils										Coconut and palm oils		Coconut and palm oils	
Nuts													
Seeds			Cocoa beans										
Legumes						Peanuts			Soybeans				
Cereal grains													
Fruits (including berries)			Coconut			Olives and avocado							
Vegetables													
Honey										N/A		N/A	
Mushrooms													

SFA=saturated fatty acid. MUFA=monounsaturated fatty acid. PUFA=polyunsaturated fatty acid. Low: < 3 g per 100 g. Medium: 3–10 g per 100 g. High: > 10 g per 100 g. Yellow to orange represents the typical content for the food group, with stronger color for higher contents. Pink represents the typical ratio for the food group, with stronger color for higher ratios. When multiple colors are seen, the content or ratio is more variable and spans several areas. Purple represents some notable exceptions within each food group. Based on nutrient values from official food databases [28, 84]. Supplementary data: nuts [85], eggs [86, 87], seafood [88–90], meats [29, 33], insects [91–94], seeds [95, 96], mushrooms [97, 98], fruits [99], vegetables [100]

constitution would be expected to yield moderately low total fat and SFA intakes. When honey is consumed with larvae, somewhat more lipids would be taken in. Based on collected dietary data, fat has been estimated to account for 13–36% of the total energy intake, with significant seasonal variation [83]. To which extent the current Hadza diet is representative of ancestral African intakes is uncertain. It probably features many of the same characteristics; however, changes in environment, culture, and lifestyle may have caused some alterations. This is true for all groups, and a limitation in terms of extrapolating characteristics of current communities to past ones. A possibility is that large game animals were more abundant in the past African landscape and diet than in the present and more depleted milieu. Low to moderate total fat and SFA intakes have also been reported for a variety of other groups, including, but not limited to, the !Kung, Tsimane, Aboriginals, and Yanomami [103–106].

Other populations have historically had a higher fat intake. The continued northward migration of *Homo sapiens* following the exodus from Africa would have engendered nutritional challenges in the form of colder climes. There is some uncertainty about the dietary characteristics of early Asian and European settlers, with scattered evidence for exploitation of different food

resources, such as megafauna (e.g., mammoths) [107–109] and grasses (e.g., cereals) [110–112], at different sites. In the well-preserved juvenile Yuka mammoth, subcutaneous fat from the hind leg has been analyzed and calculated to have originally contained approximately 1/4 PA (C16:0) and SA (C18:0), combined, with the bulk of the rest of the FAs being MU and PU [113]. Similar values were obtained for frozen hind leg fat from ancient horses, whereas belly fats from bison were found to be more enriched in SFAs [113]. These types of fat deposits may have been significant energy sources in certain areas, particularly those in which plant growth and carbohydrates were less abundant.

More research is required to elucidate the diet composition of Cro-Magnon and other non-African human ancestors, as well as the nutritional biological imprint left on descendants. Falling temperatures and glacial expansion of the last ice age would have forced a greater reliance on animal source foods, particularly in northern areas and during parts of the year. However, there is evidence that various southern refugia functioned as a safe harbor for groups of humans that later went on to populate more northern areas of Eurasia as the temperatures rose following the last glacial maximum some 20.000 years ago [114, 115]. Moving further away from equator, to higher latitudes, correlates with increasing HG fat/carbohydrate ratio [116]. An extreme example is the Inuit, whose traditional diet consists mainly of animals, and in particular sea-dwelling creatures. While being high in total fat, much of the fat is of the unsaturated type, with high concentrations of the n-3 PUFAs eicosapentaenoic acid (C20:5) and docosahexaenoic acid (C22:6) found in Eskimo food [117, 118]. Another group consuming a higher fat diet is the Maasai, whose pastoral subsistence revolves heavily around meat, milk, and blood from herded animals [119]. The diet has been estimated to contain approximately 2/3 fat as a proportion of total calories, supplying fairly high amounts of SFAs [119].

Besides dairy and meats from livestock, coconut is a SFA rich food. In this regard, it is unusual among vegetable foods, which generally contain little saturated fat. In 1989 and into the 1990s, the late Swedish researcher Staffan Lindeberg conducted a survey of the health condition and diet of the Kitavan islanders in Papua New-Guinea. Among the foods consumed, coconuts contributed significantly to the overall diet, with the three other dietary staples being fruit, fish, and tubers [120]. A rough intake estimate of 40 g of daily saturated fat from coconut was made by Lindeberg et al., with saturated fat thus contributing approximately 17% of total calories [120]. The coconut, which also features in the diets of other equatorial groups, contains predominantly lauric acid (LA) (C12:0), as opposed to SFAs with a longer chain length, which are more concentrated in animal source foods. To which extent coconut was a part of humans' ancestral nutritional matrix requires further investigation.

Effects

SFAs can be produced endogenously and are not considered essential nutrients to be ingested, as no minimal intake requirement or overt deficiency symptoms have been identified. This implies that *Homo sapiens* have not evolved a dependence on regular or high SFA consumption. However, it does not exclude the possibility that very low intakes can have undesirable effects, with some research emphasizing significant cellular and physiological roles of SFAs (e.g., pertaining to protein acylation, gene transcription, and PUFA bioavailability) [121, 122]. These functions can be maintained by lipogenesis from precursor material (e.g., glucose) catabolized to acetyl CoA; however, the production of certain SFAs, most notably myristic acid (MA) (C14:0), may be insufficient to completely meet demand. While noteworthy, and a potential issue in situations of long-term energy deficit and restrictive vegan dieting, the capacity for endogenous production, coupled with the widespread presence of SFAs across the plant and animal kingdom, make insufficiency unlikely in most cases. Rather than discovering and investigating deficiency existences and symptoms, research in the area has principally revealed and been concerned with potential adverse effects of saturated fat consumption.

LDL and cardiovascular disease risk

While certain studies have not found evidence of adverse cardiovascular effects [1–4], others do show unfavorable outcomes [123–126]. As an example of the former, a 2017 cohort study published in *The Lancet* found no association between saturated fat intake and major cardiovascular disease, myocardial infarction, or cardiovascular disease mortality among 135 335 individuals from 18 countries [127]. However, a 2020 updated Cochrane review of RCTs found evidence that reducing saturated fat intake for at least two years causes a potentially important reduction in combined cardiovascular events [124]. Studies attempting to ascertain the effects of specific food groups (e.g., dairy) and their fat also show some variation in reported cardiovascular outcomes [128–131].

The somewhat heterogenous findings in the area are connected to the intrinsic difficulty of accurately assessing the effects of particular nutrients and their sources on long-term health and disease outcomes. Much of the data comes from prospective cohort and other observational studies, which have major limitations compared to RCTs. There is a high risk of unmeasured and residual confounding, imprecise dietary data collection methods may be used, and a wide variety of foods are consumed by the

participants. The impact of a lower intake of a particular food type or nutrient would be expected to depend on the nature of the replacement consumption, a facet that is both difficult to control and adjust for over the lengths of time leading up to cardiovascular morbidity and mortality. Hence, soft endpoints are frequently utilized as surrogates.

The effect of saturated fat on cardiovascular events is commonly attributed to LDL-C increases followed by accumulation in atherosclerotic plaque, arterial narrowing with decreased nutrient and oxygen passage, and thrombogenesis with concomitant risk of heart attack and stroke. A causal relationship between LDL-C and cardiovascular disease is appreciable from several lines of evidence [132, 133], making population lipoprotein data relevant to health and risk assessments. Contemporary Americans have total cholesterol (TC) and LDL-C levels greatly exceeding those of HGs and other free-living primates (e.g., baboons, monkeys) [134, 135]. In a 2004 analysis, the normal LDL-C concentrations of the latter were asserted to be in the range of 50 to 75 mg/dl, as opposed to approximately 130 mg/dl in the former [134]. Other known heart disease risk factors, such as high body mass index and blood pressure, are generally absent or negligible as well [14, 135, 136]. In the Hadza, superb markers of circulatory health have been reported [136, 137]. Excluding early deaths, and despite limited or no access to modern medical advancements, it is not uncommon for foragers to reach older ages, with a modal age of adult death of 65–75 years reported in the cross-cultural examination by Gurven & Kaplan [138], highlighting that the favorable characteristics are not due to a lack of elders.

Cholesterol values intermediate to those in HG communities and industrialized societies have been reported in horticultural, farming, and pastoral populations [15, 106, 120, 139, 140]. As compared to Swedes, Lindeberg et al. found that TC was lower for Kitavan males, as well as for women over 60 years of age [120]. There is evidence to suggest that the primary LDL-C-raising FAs are MA (C14:0) and PA (C16:0) [141, 142]. In a meta-analysis of 60 controlled trials, LA (C12:0) was found to predominantly raise high-density lipoprotein (HDL), which is involved in cholesterol efflux and removal to the liver [143]. In comparison to the Swedish reference sample, the LDL/HDL cholesterol ratio of the Kitavans was markedly lower in both men and women over 60 years of age, with no significant difference in the lower age brackets. The reported cholesterol values for this population are relatively high as compared to other preindustrial groups, but overall there was a striking absence of traditional cardiovascular risk factors [120, 144], accompanied by no detected cases of stroke or ischaemic heart disease [145]. To which extent non-dietary factors, such as routinely utilized tobacco, affected the lipid values and ratios, and if the Kitavans have genetically adapted to coconut fat, is uncertain.

The Tsimane, a Bolivian farming-foraging population that has recently been the subject of some research, have mean TC and LDL-C concentrations of 151 mg/dl and 91 mg/dl, respectively [139]. They have elevated C-reactive protein (CRP) levels, due to a high parasite burden, yet little coronary atherosclerosis [139]. Other groups with a mixed subsistence strategy, such as the Yanomami and Kren-Akorore Indians, exhibit even lower cholesterol concentrations, in the range seen in pure HGs [106, 146]. In that low range, the Inuit are at the higher end [134]. There have been ultrasonographic and autopsy reports of atherosclerosis both in the traditional Inuit and the Maasai, yet low rates of cardiovascular complications and mortality [147–149]. This points to physiologic mechanisms and/or lifestyle factors (e.g., high n-3 PUFA consumption, rigorous physical activity) exerting a protective influence. The Maasai show an unusual capacity for downregulating endogenous cholesterol synthesis in response to higher intakes [119]. They have relatively low mean TC of 135 mg/dl [140], as compared to values closer to or exceeding 200 mg/dl in industrialized countries like Croatia, Finland, Germany, Austria, Greece, Italy, Netherlands, and the U.S [150, 151]. The overall pattern is depicted in Fig. 3.

Different factors can cause and contribute to cholesterol elevation, including obesity, physical inactivity, and cigarette smoking [152]. SFA consumption is also a relevant factor [123, 124, 143, 153, 154]. Replacing SFAs with UFAs lowers cholesterol [124, 154–157]. In a WHO systematic review and regression analysis of 84 studies with a randomized parallel or crossover design and thorough control of food intake, replacing 1 E% from SFAs with an equivalent amount of *cis*–PUFAs significantly decreased TC by 0.064 mmol/l (2.47 mg/dl) and LDL-C by 0.055 mmol/l (2.12 mg/dl) [156]. Replacement with *cis*-MUFA yielded slightly lower reductions, of -0.046 mmol/l (1.78 mg/dl) TC and – 0.042 mmol/l (1.62 mg/dl) LDL-C. Substituting with carbohydrate also produced significant reductions, but to a somewhat smaller extent. The mechanisms linking higher SFA to higher LDL remain to be fully elucidated but appear to involve decreased LDL receptor activity [158, 159].

The cholesterol-reducing effects were detected across a range of SFA intakes, including ones below 10% of total energy intake. According to these data, having 4 E% in the form of PUFAs rather than SFAs could translate to 10 mg/dl lower TC and 8.5 mg/dl lower LDL-C, with a somewhat smaller difference for SFAs versus MUFAs or carbohydrate. The nutrient categories included mixtures of compounds, such as monosaccharides, disaccharides, and polysaccharides in the carbohydrate category. The effects on cholesterol may vary depending on which

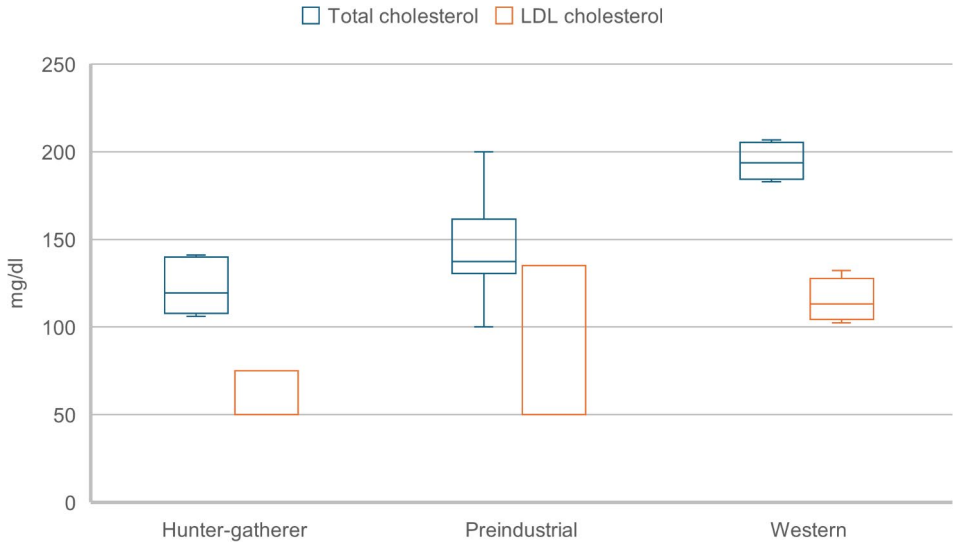

Fig. 3 Ranges and medians of mean circulating cholesterol values of different population types: Hunter-gatherer (Hadza, Inuit, Aborigines, Pygmy, San) [15, 134], Preindustrial (horticulturalists, farmer-foragers, and pastoralists) [15, 106, 120, 139, 140], and Western (United States, Canada, Australia, and Western European nations) [151]. Values are unadjusted for age and sex. When LDL cholesterol (LDL-C) measurements were not available, estimates were made on the basis of measured total cholesterol (TC). Hunter-gatherer LDL-C estimates are from O'Keefe et al. [134]. Preindustrial LDL-C range spans from 50% of the lowest TC measure of 100 (in the Brazilian Kren-Akorore Indians) to the measured LDL-C value of 135 in the group with the highest measured TC (the Kitavans in Papua-New Guinea). Western LDL-C values are all measured

of these are consumed, however, the included studies did not provide sufficient dietary information for analyzing such distinctions. It is noted that low-glycemic index diets have previously been found to reduce TC and LDL-C to a greater extent than high-glycemic ones [160].

It is difficult to estimate the precise and total effects of the substitutions on cardiovascular outcomes, due to the length of time it takes for cardiovascular disease to develop, differential responses (e.g., due to different initial cholesterol levels), subsets of LDLs unevenly affecting heart disease risk [161, 162], and other physiological effects of altering the fatty acid intake. Pooled data from experimental statin studies suggest that 1 mmol/l (38.67 mg/dl) LDL-C reduction corresponds to a little over 20% reduced risk of major vascular events over 4–5 years [163–165], implying a ~5% lowered risk from reducing LDL-C by 8.5 mg/dl. While indicative of the effect of LDL-C change, the number is unlikely to represent the full and true cardiovascular influence of replacing SFAs with other nutrients. Higher SFA consumption is associated with other components of dyslipidemia (e.g., triglyceride elevation) in addition to LDL-C elevation, while certain other FAs, most notably n-3 PUFAs, show inverse protective effects [156, 166, 167]. The progressive nature of atherosclerosis also implies that the effects of lipid alterations may accrue and manifest over time.

Overall, the evidence suggests that current western cholesterol values are abnormally high from an evolutionary point of view and that lowering the levels will benefit cardiovascular health. In stark contrast to the absence or rarity of heart disease frequently reported for unacculturated traditional groups [15, 139, 145], postindustrial societies suffer at epidemic proportions. It is currently the leading cause of death worldwide [168], underscoring the importance of sound etiological understanding and effective prevention. Reducing saturated fat intake is one viable measure; however, additional interventions (e.g., weight loss, physical activity) would be required to approach ancestral standards.

Endotoxemia and inflammation

Another line of research concerns the effects of SFAs on gut microbiota and immune system activity. Repeated experiments, with different designs and food products, have linked high SFA intakes with endotoxemia and inflammation [169–174]. A single high-SFA meal elicits a response, with significantly elevated endotoxin levels [170, 171]. UFAs (particularly PUFAs) do not produce the same result [169, 170, 172, 174]. The consistency of the pattern across multiple studies suggests that it is not dependent on particular conditions but represents a true and relevant difference. Endotoxins originate from gram-negative bacteria, implying that high-SFA distorts gut microbiota composition and/or increases endotoxin absorption from the intestine. They are sensed by and activate toll-like receptor 4, inciting an inflammatory response [175, 176].

While shorter-chain SFAs such as caprylic acid (C8:0) and LA (C12:0) have antimicrobial activity, longer chain SFAs do not exhibit the same influence, and may in some instances favor the growth of opportunistic pathogens, leading some researchers to theorize that they could

trigger an inflammatory response by acting as warning signals of impeding gut microbial alteration and danger [177]. In one small but noteworthy study published in the *British Journal of Nutrition*, the immunological effects of fatty SFA-rich modern wagyu meat was compared with that of lean low-SFA traditional kangaroo meat [178]. Interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and CRP were significantly elevated postprandially to the first meal as compared to the second. While it cannot be decisively concluded that the effects were due to saturated fat, it is likely, in light of other data, that it was a significant factor.

The inflammatory effects plausibly contribute to high-SFA-induced dyslipidemia, as lipoprotein alterations are commonly seen in situations of infection and inflammation, serving a protective function, yet promoting atherosclerosis over the long term [179–181]. Inflammation is critically involved at all stages of arterial plaque development and dysfunction [176, 182], with statins likely exerting some of their effects through anti-inflammatory influence [183–185]. Another widespread issue that involves inflammatory pathways is acne vulgaris. Currently endemic in westernized societies, this aesthetically and psychologically straining skin disease is reported to have been absent among the Aché, the Inuit, the Kitavans, and the Okinawans, as well as much less common in other traditional and rural groups [18, 186]. Dietary factors are important in the pathogenesis, with PA (C16:0) emerging as a contributing factor to the inflammatory aspects [187, 188]. Other conditions that have increased dramatically in prevalence, such as diabetes and depression, also have inflammation in their pathogenesis [189–191]. In both, endotoxins are capable inducers [192–195]. Chronic inflammation is a common denominator of diseases of civilization [196–198], implicated in several different types of disorders (Fig. 4).

Limited data from traditional groups show some variation in inflammatory markers, with median CRP values ranging from 0.5 mg/l in Shuar and Kitavan forager-horticulturalists [207, 208], across values closer to or exceeding 1 mg/l in rural Ghanaians and the Hadza [136, 209], to 3 mg/l or more in the Tsimane [139, 210]. As compared to the Dutch and Swedish reference samples, the CRP levels in the Ghanaians and Kitavans were significantly

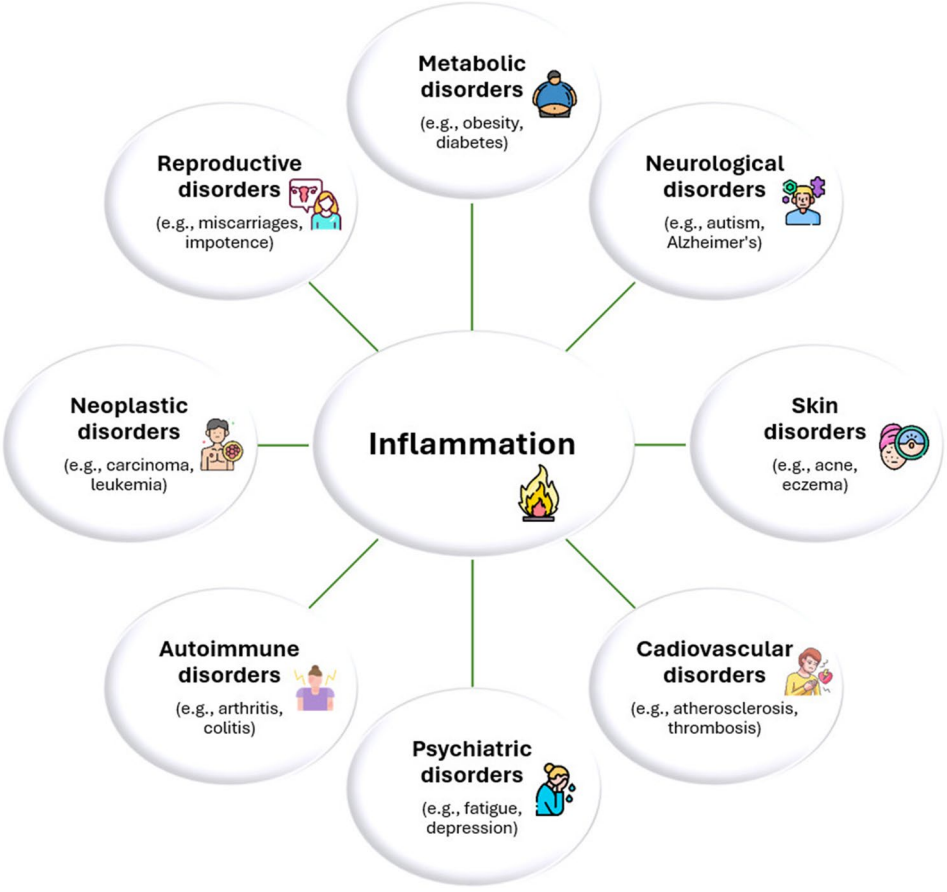

Fig. 4 Some diseases and issues associated with chronic inflammation. Connections are reviewed in overview articles [196–198], as well as publications on autism [199], Alzheimer's [200], acne [187], eczema [201], atherosclerosis & thrombosis [182], fatigue [202], depression [190], arthritis & colitis [203], carcinoma & leukemia [204], miscarriages [205], impotence [206], and obesity & diabetes [189]

lower [208, 209], while the opposite is true for the Tsimane as compared to people in the United States [210]. The high CRP in the Tsimane, yet low rates of chronic degenerative disease, suggests unique adaptation (e.g., to specific pathogen loads) and/or protective lifestyle factors (e.g., low-SFA, high-fiber diet). Elevated CRP and/or cytokine levels have been found in disorders such as obesity, prediabetes, depression, and chronic fatigue syndrome [191, 202, 211, 212], suggesting low-grade chronic inflammation among significant proportions of contemporary industrialized populations.

Inflammation is energetically costly, requiring significant nutritional support for the activated immune system, redirecting priorities and resources away from physical function and reproduction towards tissue repair and homeostatic restoration; hence, chronic activation would have constituted a significant fitness disadvantage in prehistoric times. It is contended that the installations and mechanisms that are active in inflammatory diseases, governing the immune activity, energy allocation, and behavioral effects, were principally selected for acute, short-term insults (e.g., infection, injury) [213, 214]. Resolution of chronic inflammation could have broad-spectrum effects, improving hormone (e.g., insulin) sensitivity, circulatory function, moods, energy levels, and reproductive capability, thereby unstraining health services, lowering medical costs, and increasing productive and healthy life years. It necessities describing and addressing proinflammatory aspects of modern diets and lifestyles, including alterations of the FA profile.

High-fat diets and health

Ketogenic and very-low-carbohydrate diets can produce rapid and meaningful fat loss [215, 216], and have been suggested to hold therapeutic promise for some diseases [217]. However, they do have nutritional shortcomings. As a result of severely restricting fruits, most vegetables, berries, and other plant foods, the intake and variation of dietary fibers and phytochemicals will be limited. This can result in gut microbiota depletion, oxidative stress, and impaired neuronal health [218–220]. Colonic fermentation of dietary fibers yields acetic acid (C2:0), propionic acid (C3:0), and butyric acid (C4:0), which lower the luminal pH, making it less hospitable to pathogens, contribute to mucosal health and integrity, serve as an energy substrate for the body, and act on the immune system and distant organs (e.g., the brain) [77, 221, 222]. Hence, a low fiber intake can compromise intestinal, general, and mental health through underproduction of short-chain fatty acids. The acquisition of micronutrients that are abundant in plant foods, but scarce or absent in animal products, such as magnesium and potassium, may also be compromised on a very-low-carbohydrate diet.

A high intake of acid-yielding animal source foods, coupled with a low intake of base-yielding fruits and vegetables, can distort acid-base balance [223–225]. Low-grade metabolic acidosis has been suggested to be a factor in current western disease, and in particular in bone and kidney disorders [223–225]. Additionally, ketoacidosis has been reported in certain cases of low carbohydrate, high fat dieting [226, 227], revealing a potential complication that physicians and dieticians should be aware of. Moving into athletic endeavors, exercisers are liable to experience fatigue and suboptimal performance and recovery when dietary fat is markedly elevated relative to carbohydrate, due to a lack of glycogen and glucose required for rapid and anaerobic energy metabolism [228, 229]. Some 300–700 g of glycogen can be stored in the muscles [230], serving as an important energy substrate particularly at higher training intensities. Yet, in cases of physical inactivity, dietary carbohydrate, and in particular refined carbohydrate, is more easily consumed in excess, causing elevated endogenous SFA production, fat gain, and risk of metabolic dysfunction with insulin resistance and hyperglycemia.

High-fat diets typically contain anywhere from 50 to 80% of the total calories in the form of fat, usually with a significant contribution from SFAs. This fat-enriched macronutrient profile is not consistent with the general pattern observed in naturally living foraging and horticulture populations [27, 64, 69, 83]. Populations with an unusually high intake of a macronutrient may present signs of good health and longevity; however, it is uncertain whether this is due to unique genetic adaptations, to which extent other factors are contributing, or if dietary adjustments could generate an even more favorable condition. In the Inuit and the Maasai, there have been reports of genetic selections related to lipid metabolism and regulation [231, 232], highlighting that general human nutritional adaptation can not be inferred from such groups with special food staples and nutrient intakes.

In nature, it is difficult to obtain extremely high fat concentrations, as wild animals tend to be (but are not always) lean. There is a protein ceiling, with intakes above approximately 35% resulting in toxicity [233], sometimes referred to as rabbit starvation. Plant fats are available and eaten in their natural form, as part of whole foods, as opposed to in the form of mechanically extracted oils. Nuts must first be foraged, and then deshelled, before consumed. Low to moderate fat concentrations, as opposed to the very high concentrations seen in oils and high-fat dairy and meats, is the norm. Being largely composed of energy-rich fat, a major intake of the latter foods would result in an overall lower fiber-, phytochemical-, and micronutrient density of the diet. A relatively high contribution of SFAs relative to UFAs would also tilt

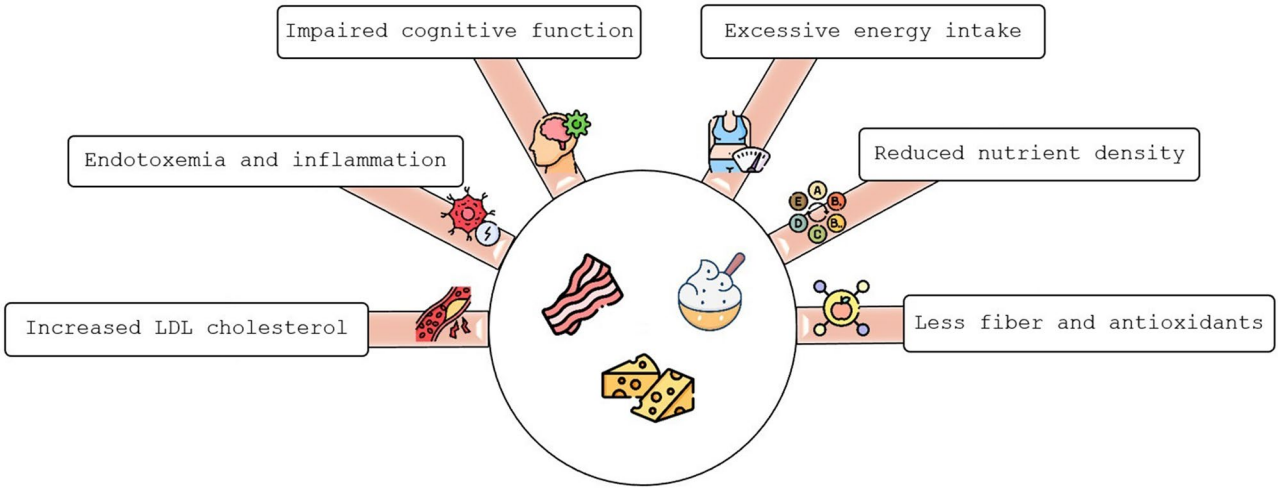

Fig. 5 Adverse effects associated with a high intake of saturated fat

the dietary ratio, potentially compromising optimal UFA intake.

In particular the long-chain n-3 PUFAs are vital for brain development and function, immune homeostasis, and chronic disease prevention. This has been extensively reviewed from an evolutionary point of view by Artemis Simopoulos, with a particular emphasis on the n-6/n-3 ratio [22, 23, 234]. Partly due to the FA compositional difference between wild and domesticated meats, but more so because of increased consumption of n-6 PUFA rich processed foods and vegetable oils, current western diets contain significantly more n-6 PUFAs relative to n-3 PUFAs, as compared to ancestral natural diets, which were more balanced in the two types [22, 23, 234]. This shift is implicated in current ill-health and disease loads [22, 23, 234]. In conjunction with the elevated SFA content, it could contribute to a proinflammatory, atherogenic, and carcinogenic potential of modern red meat products. Consistent with evolutionary prediction, substitution trials have found less favorable or adverse effects when SFAs are replaced with mostly n-6 relative to n-3 PUFAs [235–237]. MUFAs like OA (C18:1), abundantly present in olive oil, nuts, and avocados, have been linked with beneficial health outcomes [238, 239]. While the cis-configuration is natural, trans FAs largely result from industrial partial hydrogenation and are widely recognized as pathogenic.

Foods with a very high fat and energy density can be less satiating than foods with a greater concentration of water, protein, and/or fiber, on a calorie-by-calorie basis [240–242]. This does not necessarily imply that fat-reduced products are superior to whole or full fat varieties, which among other things may provide more fat-soluble vitamins; however, it does suggest that significant consumption of high-fat foods could undermine the nourishing capacities of the diet and contribute to excessive energy intakes, fat gain, and obesity. Comparing contemporary western diets with ancestral natural diets, a striking contrast is the relatively higher energy density of the former, owing largely to the inclusion of food products with a very high concentration of sugar and/or fat (e.g., chocolate, potato chips, cheese, bacon). As compared to butter (744 kcal per 100 g), a food like sweet potatoes is remarkably low in calories, only providing about 80 kcal per 100 g [28]. Both inflammation and food, fat, and energy overconsumption have been linked with cognitive impairment and neurodegenerative disease [73, 200, 243–245]. This helps explain why SFA rich diets have been associated with such outcomes [246–252]. When isocaloric meals are consumed, SFA rich consumption causes cognitive impairment over and beyond that of MUFA consumption [250, 251], implying that SFA boluses are inherently more challenging for the brain. Alas, a previously adaptive propensity to seek fat and energy-richness appears a liability in dietary conditions of abundance, highlighting a need for education, communication, and intervention guiding healthy consumer choices.

The effects of SFAs on function and health will invariably depend on the amount, type, and product that is consumed, as well as factors such as microbiota and dietary composition. More research, with different interventions and participants, are required to more fully elucidate the relationships. An overview of the discussed adverse effects is provided in Fig. 5.

Conclusions

The discussion and controversy regarding fat and SFAs has largely revolved around epidemiological research, which is valuable, but prone to discrepancy and bias. It can benefit from evolutionary insights. Unknowingly, Charles Darwin provided a sound basis for nutritional

investigation and conversation. Through the lens of evolution, an understanding of what constitutes appropriate nutrient intake levels, matched with the naturally selected human biology, may be achieved. Ancestral human diets have varied temporally and spatially; however, systematic food and diet analyses can reveal nutritional patterns that may serve as a template for contemporary evaluations and recommendations.

High and increasing rates of diet-related dysfunction and disease highlight that nutritional changes have greatly outpaced genetic accommodation. Diet-related issues can affect fertility, but many (e.g., degenerative diseases associated with excessive and/or altered fat consumption) develop over a long time, involve a myriad of genes, manifest later in life, and have little or no impact on reproductive outcomes under recent and present conditions; hence, they are not rapidly eliminated by natural selection. Issues that are more acute and/or debilitating (e.g., indigestion of lactose) have spurred documented adaptations, but these are of a quite specific nature, not covering the range of effects novel diets and food types have on the organism. Recognizing and addressing insidious incongruences is of vital importance to public health in the 21st century.

As for SFAs, this subset of lipids has been consumed by human ancestors both recent and prehistoric. However, the densest dietary sources did not become available until fairly recently. Such products, which primarily include high-fat meat and dairy products from domesticated animals, generally contain supernormal concentrations of SFAs relative to the foods that have been consumed evolutionarily, and that are still consumed by groups practicing hunting, gathering, and horticulture. A major intake of these products distorts the FA profile of the diet; increases chronic disease risk through cholesterol elevation, inflammation, and cognitive dysfunction; and takes up space that could otherwise have been filled by more nutrient-dense and satiating foods. In advocating and designing dietary patterns, it appears prudent to prioritize foods with significant amounts of n-3 PUFAs, while restricting items with a very high n-6 PUFA or SFA content. Examples of non-SFA rich food types are seafood, avocados, olive oil, nuts, and seeds. Provided the diet contains a variety of natural whole foods, a balance between SFAs, MUFAs, and PUFAs will be attained.

For environmental and health reasons, public dietary guidelines are increasingly recommending higher plant food consumption relative to animal source foods. This necessarily entails a lower SFA intake and recommendation than if more animal-based diets were to be encouraged. The upper limit for what constitutes an acceptable SFA intake is up for debate. The evolutionary perspective offered here implies that it is in the vicinity of what is already recommended. For individuals and groups requiring and/or benefitting from caloric density, such as hard-training athletes, small children, and elders with low appetite, higher intakes of SFAs may be warranted; however, in general, a more restricted intake appears advisable.

Abbreviations

CRP	C–reactive protein
HDL	High–density lipoprotein
HG	Hunter–gatherer
LA	Lauric acid
LDL-C	Low–density lipoprotein cholesterol
MA	Myristic acid
MUFA	Monounsaturated fatty acid
PA	Palmitic acid
PUFA	Polyunsaturated fatty acid
SA	Stearic acid
SFA	Saturated fatty acid
TC	Total cholesterol
UFA	Unsaturated fatty acid
WHO	World health organization

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