

The western diet and lifestyle and diseases of civilization

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Abstract: It is increasingly recognized that certain fundamental changes in diet and lifestyle that occurred after the Neolithic Revolution, and especially after the Industrial Revolution and the Modern Age, are too recent, on an evolutionary time scale, for the human genome to have completely adapted. This mismatch between our ancient physiology and the western diet and lifestyle underlies many so-called diseases of civilization, including coronary heart disease, obesity, hypertension, type 2 diabetes, epithelial cell cancers, autoimmune disease, and osteoporosis, which are rare or virtually absent in hunter-gatherers and other non-westernized populations. It is therefore proposed that the adoption of diet and lifestyle that mimic the beneficial characteristics of the preagricultural environment is an effective strategy to reduce the risk of chronic degenerative diseases.

Keywords: Paleolithic, hunter-gatherers, Agricultural Revolution, modern diet, western lifestyle and diseases

Introduction

The physical activity, sleep, sun exposure, and dietary needs of every living organism (including humans) are genetically determined. This is why it is being increasingly recognized in the scientific literature, especially after Eaton and Konner's¹ seminal publication in 1985, that the profound changes in diet and lifestyle that occurred after the Neolithic Revolution (and more so after the Industrial Revolution and the Modern Age) are too recent on an evolutionary time scale for the human genome to have fully adapted.¹⁻²⁷

In fact, despite various alleles being targets of selection since the Agricultural Revolution,²⁸⁻⁴² most of the human genome comprises genes selected during the Paleolithic Era⁴³ in Africa,⁴³⁻⁵⁹ a period that lasted from about 2.5 million years ago to 11,000 years ago.¹⁴ Indeed, anthropological and genetic studies suggest that all human beings living in Europe, Asia, Oceania, and the Americas share a common African *Homo sapiens* ancestor.⁴⁷⁻⁵⁷ This concept is corroborated by data showing that there is less genetic diversity throughout the world's non-African population than there is within Africa itself.^{44-46,53,57,58}

Moreover, many of the selective pressures underlying these postagriculture alleles were not induced by changes in sleep, exercise, and diet but rather by pathogens, fatal diseases, and harsh environments,^{28-31,37-39} with a few key exceptions.^{41,42} One of those exceptions pertains to alleles of the LCT gene (which codes for the enzyme lactase-phlorizin hydrolase [LPH]) that give rise to the phenotype of adult lactase persistence (ALP).⁶⁰ These LPH-encoding alleles were initially selected in populations with a long history of milk and dairying, such as north-western Europeans and some sub-Saharan

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African and Bedouin pastoralists. Today, ALP occurs in about 35% of the world's population.⁶⁰

The impetus for these genetic changes was not to increase longevity and resistance to chronic degenerative diseases but rather to increase the probability of survival and reproductive success.^{27,61,62} Occasionally, mutations that had positive survival and reproductive value sometimes also caused adverse health effects in the postreproductive years.^{4,27,61,62} Furthermore, single gene mutations, although relevant for physicians when treating an individual patient, are imperfect models to prevent chronic degenerative diseases whose clinical symptoms normally affect the postreproductive years and involve numerous genes.⁶¹

Importantly, 11,000 years represent approximately 366 human generations,⁶³ which comprise only 0.5% of the history of the genus *Homo* (Table 1).^{14,63–65} Indeed, the Industrial Revolution and the Modern Age, which mark the beginning of the western lifestyle, represent only seven and four human generations, respectively (Table 1),^{14,63–65} and were marked by rapid, radical, and still ongoing changes in lifestyle and diet,^{14,65} coupled with improved public health measures that greatly reduced mortality in the prereproductive years (and hence largely eliminated impaired reproductive fitness as a selection pressure).^{62,66} As such, it is highly unlikely that genetic adaptations that allow us to thrive on a western diet and lifestyle have occurred.

Health status of preagriculture traditional populations

The idea that modern *Homo sapiens* are still adapted to an ancestral environment is reinforced by data showing that hunter–gatherers, and other populations minimally affected by modern habits, exhibit superior health markers, body composition, and physical fitness compared with industrialized populations, including:

1. Low blood pressure in hunter–gatherers and horticulturalists (Table 2)^{26,67–69} when compared with current optimal values defined by health institutions (<120 mm Hg

Table 2 Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at age 40–60 years in hunter–gatherers and horticulturalists (mm Hg)^{26,67–69}

Population	Men		Women	
	SBP	DBP	SBP	DBP
Bushmen	108	63	118	71
Yanomamo	104	65	102	63
Xingu	107	68	102	66
Kitava	113	71	121	71

and <80 mm Hg for systolic blood pressure and diastolic blood pressure, respectively)⁷⁰

2. Lack of association between blood pressure and age in hunter–gatherers (Table 3)⁶⁹ and horticulturalists⁶⁸ compared with in North Americans and Swedes^{26,68,70}
3. Persisting excellent insulin sensitivity among middle-aged and older individuals in non-westernized traditional populations that maintain their ancestral lifestyle^{26,71–81}
4. Lower fasting plasma insulin concentrations and higher insulin sensitivity (measured by the Homeostatic Model Assessment [HOMA] index) in the horticulturalists of Kitava (Papua New Guinea) compared with in healthy Swedes (Figures 1 and 2, respectively)⁷⁴
5. Lower fasting plasma leptin in the horticulturalists of Kitava and the Ache hunter–gatherer Indians of Paraguay compared with in healthy Swedes⁸² (Figure 3) and North American male distance runners⁸³ (Figure 4), respectively
6. Lower body mass index (BMI) in hunter–gatherers, traditional pastoralists, and horticulturalists²⁶ compared with in westerners.^{26,84} For instance, as observed by Lindeberg,²⁶ in Kitava, 87% of men and 93% of women aged 40–60 years had a BMI below 22 kg/m² and not a single individual in this age group was overweight or obese²⁶
7. Lower waist (cm)/height (m) ratio in the horticulturalists of Kitava compared with in healthy Swedes (Figure 5)⁸²
8. Lower tricipital skinfold (mm) in hunter–gatherers compared with in healthy Americans⁶⁷ (Figure 6)

Table 1 Historical milestones in human generations^{14,63–65}

Historical milestones	Generations	% total
<i>Homo habilis</i>	76,667	100.0
<i>Homo erectus</i>	60,000	78.2
Modern <i>Homo sapiens</i>	6666	8.7
Neolithic Revolution	366	0.48
Industrial Revolution	7	0.009
Food industry (junk food) and physical inactivity (Modern Age)	4	0.005

Table 3 Systolic blood pressure and diastolic blood pressure in Yanomamo Indians (mm Hg)⁶⁹

Age (years)	Men	Women
0–9	93/59	96/62
10–19	108/67	105/65
20–29	108/69	100/63
30–39	106/69	100/63
40–49	107/67	98/62
50+	100/64	106/64

9. Greater maximum oxygen consumption ($\text{VO}_2 \text{ max}$) in hunter-gatherers and traditional pastoralists compared with in average Americans⁶⁷ (Figure 7)
10. Better visual acuity in hunter-gatherers and other traditional populations minimally affected by western habits compared with in industrialized populations⁸⁵
11. Better bone health markers in hunter-gatherers compared with in western populations and even traditional agriculturalists^{26,86–98}
12. Lower fracture rates in non-westernized populations compared with in western populations.^{26,96–99}

Another line of evidence supporting the superior health markers of hunter-gatherers and other traditional populations comes from the historical records of explorers, adventurers, and frontiersmen, which invariably described the populations they encountered as being healthy, lean, fit, and free of the signs of chronic degenerative diseases.²⁶ But perhaps even more important than these observations are the medical and anthropological reports showing a low incidence of chronic degenerative diseases such as metabolic syndrome and type 2 diabetes,^{26,67,73,74,100} cardiovascular disease (CVD),^{26,65,67,68,100–112} cancer,^{26,67,113–118} acne,¹¹⁹ and even myopia⁸⁵ in hunter-gatherers, traditional pastoralists, and horticulturalists compared with in western populations^{26,65,67,85,100,108,109,113,114,119,120} and even ancient Egyptians^{67,114,121–123} and medieval Europeans.¹¹⁴

Counterarguments

It has been argued that traditional populations may have been genetically protected against the chronic degenerative diseases that occur in industrialized countries, yet when non-westernized individuals adopt a more contemporary lifestyle, their risk for chronic degenerative diseases is similar or even increased compared with modern populations.^{26,67,78–80,108,109,124–144} Further, when they return to their original traditional lifestyle, many disease

markers or symptoms return to normal.^{81,145} These data demonstrate that the superior health markers, body composition, and physical fitness of hunter-gatherers and other populations minimally affected by modern habits are not due primarily to genetics but first and foremost to the environment. These studies also indicate that few or no genetic adaptations have occurred to protect any population from chronic diseases that are elicited by modern diet and lifestyles.

Indeed, two different individuals when exposed to the same modern environment (eg, western diet, physical inactivity, insufficient and inadequate sleep, chronic psychological stress, insufficient or excessive sun exposure, use of recreational drugs, smoking, pollution) will probably express a suboptimal phenotype.^{27,65,146,147} This may or may not be considered pathological, depending on genetic variants (eg, haplotypes, single nucleotide polymorphisms, microsatellites, simple sequence repeats, insertion/deletion, copy number variations) and differences in gene expression regulation (such as epigenetic variations).^{27,62,146,148}

Another common counterargument is the short average life expectancy at birth of hunter-gatherers. The problem with this marker is that it is influenced by fatal events (eg, accidents, warfare, infections, exposure to the elements) and childhood mortality. Today, average life expectancy is higher not because of a healthier diet and lifestyle but owing to better sanitation, vaccination, antibiotics, quarantine policies, medical care, political and social stability, and less physical trauma.⁶⁶ Moreover, Gurven and Kaplan,¹⁴⁹ in a recent assessment of the mortality profiles of extant hunter-gatherers for which sufficient high-quality demographic data exist, concluded that “modal adult life span is 68–78 years, and that it was not uncommon for individuals to reach these ages”.

Of more importance, these individuals reached age 60 years or beyond without the signs and symptoms of chronic degenerative diseases that afflict the majority of the elderly in industrialized countries.⁶⁶ Furthermore, in western countries, various illnesses and conditions, such as obesity, type 2 diabetes, gout, hypertension, coronary heart disease (CHD), and epithelial cell cancers, which are rare or virtually absent in hunter-gatherers, horticulturalists, and traditional pastoralists, are now increasing in younger age groups.^{26,64–66} Finally, the fossil record suggests that when hunter-gatherer populations made the transition to an agricultural pattern of subsistence, their health status and lifespan decreased.^{26,109,150}

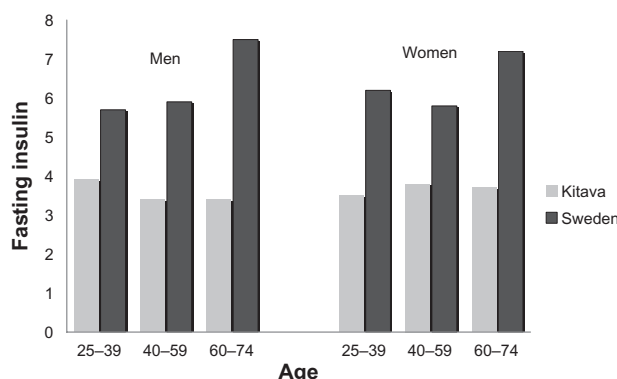


Figure 1 Fasting plasma insulin (IU/mL) in Kitava horticulturalists versus in healthy Swedes.⁷⁴

The ancestral environment

With the help of anatomical, biomechanical, and isotopic analyses of various hominin skeletons, the archaeological

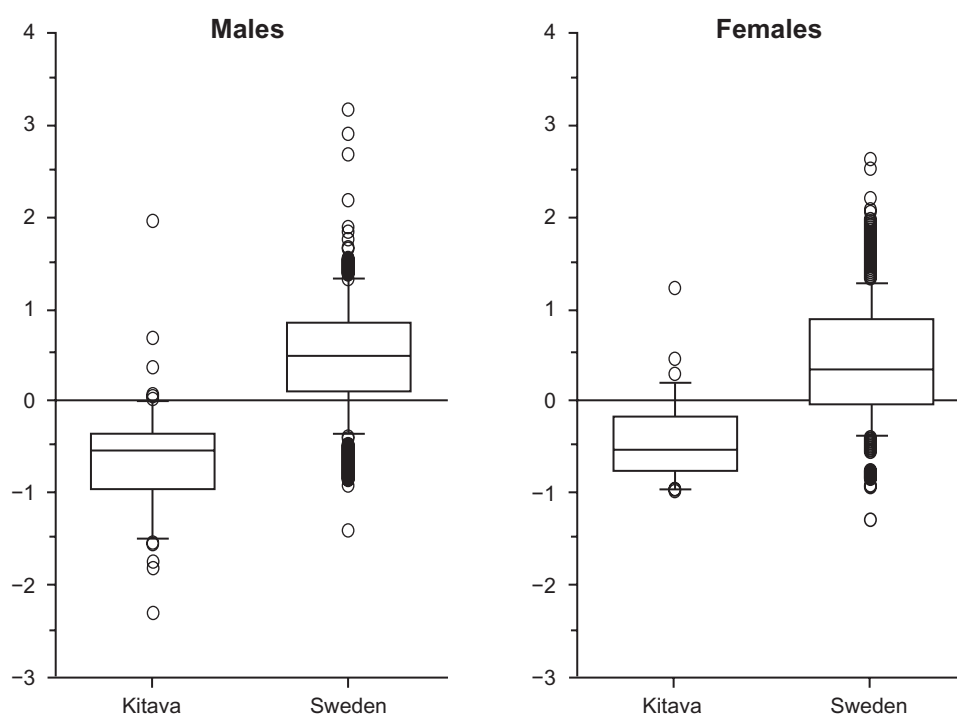


Figure 2 Homeostatic Model Assessment Index in Kitava horticulturalists versus in healthy Swedes.⁷⁴

and geological evaluation of their habitats, and ethnographic studies of various hunter–gatherer societies (whose diet and lifestyle resembled the Palaeolithic diet and lifestyle), it was concluded^{138,61,64,65,108,151–157} that, despite the existence of different diets and lifestyles, which varied due to differences in geography, ecological niche, season, and glaciations, they all had the following characteristics:

- Regular sun exposure^{38,151} (except for the Inuit, whose very high intake of vitamin D3 from fish and marine mammals^{158,159} may have rendered the lack of ultraviolet-stimulated cutaneous vitamin D synthesis less relevant)
- Sleep patterns in synch with the daily variation in light exposure¹⁵²

- Acute as opposed to chronic stress¹⁶⁰
- Regular physical activity, as this was required to obtain food and water, to escape from predators, for social interaction, and to build shelters^{146,147,153}
- Lack of exposure to man-made environmental pollutants¹⁶⁰
- Universal fresh (generally unprocessed) food sources as depicted in Table 4.^{14,64,65,154,155,157}

The Neolithic and industrial revolutions and their consequences

The Agricultural Revolution began about 11,000 years ago in the Middle East, later spread to other regions of the

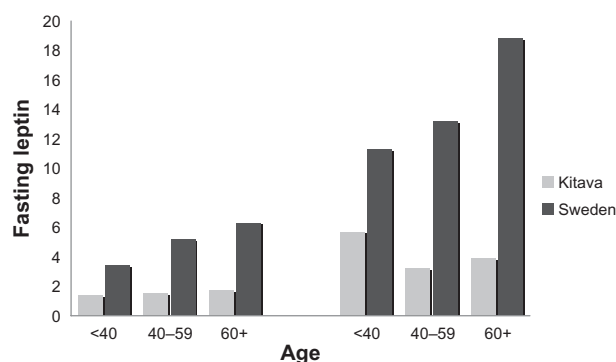


Figure 3 Fasting plasma leptin (ng/mL) in Kitava horticulturalists versus in healthy Swedes.⁸²

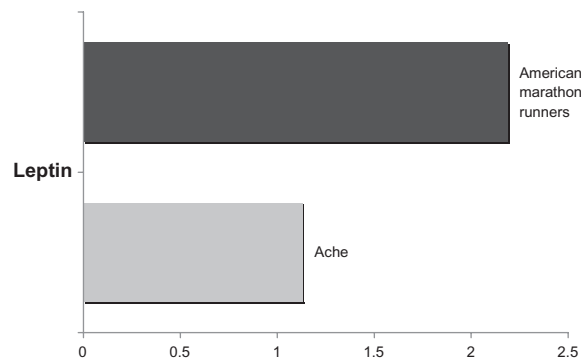


Figure 4 Fasting plasma leptin (ng/mL) in Ache Indians versus in American marathon runners.⁸³

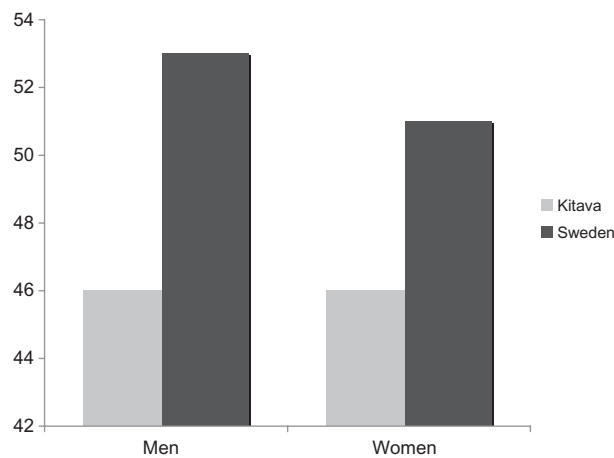


Figure 5 Waist circumference (cm)/height (m) in Kitava horticulturalists versus in healthy Swedes.⁸²

globe,^{14,65,154} and drastically altered the diet and lifestyle that had shaped the human genome for the preceding 2 million plus years. Some of the more significant dietary changes were the use of cereal grains as staple foods, the introduction of nonhuman milk, domesticated meats, legumes and other cultivated plant foods, and later widespread use of sucrose and alcoholic beverages.^{14,65}

Nevertheless it was the Industrial Revolution (with the widespread use of refined vegetable oils, refined cereal grains, and refined sugars)^{14,65} and the Modern Age (with the advent of the “junk food” industry, generalized physical inactivity, introduction of various pollutants, avoidance of sun exposure, and reduction in sleep time and quality coupled with increased chronic psychological stress)^{14,38,65,146,152,153,160} that brought about the most disruptive and maladaptive changes, which may have serious pathophysiological consequences. For instance, chronic psychological stress, environmental pollution, and smoking are associated with low-grade chronic inflammation,^{161–165} which is one of the main causes of insulin resistance.^{161,164,165}

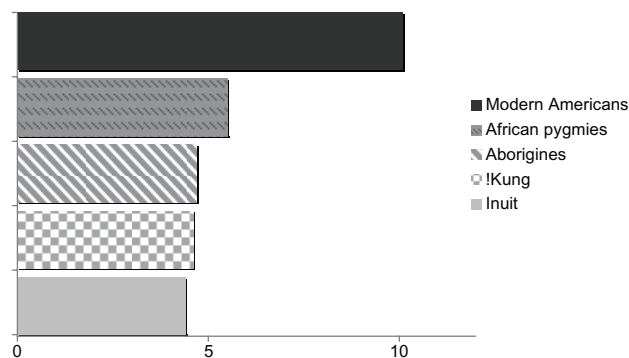


Figure 6 Tricipital skinfold (mm) in several populations.⁶⁷

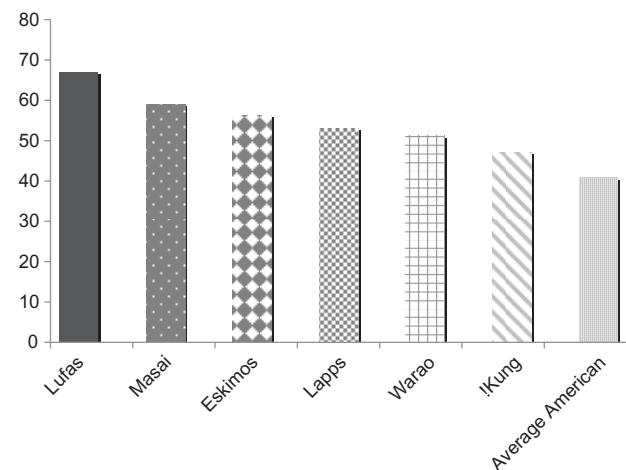


Figure 7 Maximum oxygen consumption in various populations (mL/kg/min).⁶⁷

Moreover, low-grade chronic inflammation is involved in all stages of the atherosclerotic process¹⁶⁶ and is being increasingly recognized as a universal mechanism in various chronic degenerative diseases, such as autoimmune diseases, certain cancers, neuropsychiatric diseases, and osteoporosis.^{27,65,160,167} Furthermore, some environmental pollutants, including pesticides and various industrial chemicals, may act as endocrine disruptors, hence being suspected of playing a causal role in hormone-dependent cancers (such as breast and prostate cancer),¹⁶⁸ insulin resistance¹⁶⁹ and type 2 diabetes,^{169,170} obesity,¹⁷¹ and CVD.^{170,172}

Insufficient sleep (fewer than 6 hours per 24-hour day) is also associated with low-grade chronic inflammation and worsening insulin resistance,^{165,173} as well as increased risks for obesity, type 2 diabetes, and CVD.^{165,174,175} This information is relevant in light of a recent cross-sectional

Table 4 Foods consumed during the Paleolithic Era^{14,64,65,154,155,157}

Foods available	Foods not available
Insects, fish, shellfish and other marine animals, reptiles, birds, wild terrestrial mammals and eggs	Dairy (except for human milk during weaning)
Plant leaves, seaweed, sea grasses and algae	Cereal grains (with the exception of occasional intake in the upper Palaeolithic)
Roots	Legumes (except certain varieties that were consumed seasonally)
Tubers	Isolated sugar
Berries and wild fruits	Isolated oils
Nuts and seeds	Alcohol
Honey (occasional intake)	Refined salt (even sea salt would be available only for shore-based populations who may have dipped their food in sea water)

population-based study showing that 28% of US adults sleep 6 or less hours per 24-hour period.¹⁷⁵ Moreover, social and work pressures, as well as exposure to artificial light at atypical biologic times (a very recent phenomenon in human evolutionary history), induce a disruption of the normal circadian rhythm, which is believed to play a key role in various diseases.¹⁷⁶ As Vgontzas et al¹⁷³ point out: “the idea that sleep or parts of it are optional should be regarded with caution”.

Perhaps even more important is the chronic vitamin D deficiency brought about by novel cultural and geographical changes in human behavior. As *Homo sapiens* left equatorial Africa and begun to occupy higher latitude regions, where the proportion of ultraviolet B wavelengths is decreased and of ultraviolet A vitamin D-destructive wavelengths is increased, previtamin D3 production became compromised (especially in the winter time).³⁸ This may have increased the incidence of rickets, muscle weakness, and bacterial and viral infections, which impaired reproductive fitness and increased early mortality.³⁸ Thus, it has been hypothesized that these were the main selective pressures for lighter skin pigmentation, which is a recent adaptation in human evolutionary history.³⁸ Although natural selection for lighter skin pigmentation may have reduced the prevalence of rickets, muscle weakness, and bacterial and viral infections, it may not have assured an optimal vitamin D status, given the many functions now attributed to 1,25-dihydroxyvitamin D (1,25[OH]2D), the existence of vitamin D receptors, and the occurrence of 1,25[OH]2D synthesis in various cells.¹⁷⁷

Today, vitamin D status is further compromised by migrations of people with dark skin (adapted to equatorial and tropical regions) to higher latitudes, and by air pollution, ozone, clothing, indoor living and working habits, and sun protection.^{38,177} Other factors contributing to a lower vitamin D status in humans include certain medications, diseases, and conditions (such as obesity, liver and kidney disease, and conditions that affect fat absorption),¹⁷⁷ and perhaps also modern dietary habits, such as a high intake of cereal grains. Epidemiological studies of populations consuming high levels of unleavened whole grain breads show rickets and vitamin D deficiency to be widespread, and high cereal diets can induce vitamin D deficiency in animals, including primates.¹⁵⁴ Moreover, as pointed out by Cordain,¹⁵⁴ a study of radiolabelled 25-hydroxyvitamin D3 (25[OH]D3) in humans consuming 60 g of wheat bran on a daily basis for 30 days showed an increased fecal elimination of 25(OH)D3, which

may progressively reduce plasma 25[OH]D3 concentrations in humans.

Reduced plasma 25[OH]D concentrations may have serious health consequences. Indeed, there is an impressive body of evidence associating low vitamin D status (measured by plasma 25[OH]D) with an increased incidence of various types of cancer (including breast, prostate, and colon), autoimmune diseases, infectious diseases, muscle weakness, osteoporosis, hypertension, insulin resistance, cardiovascular, and all-cause mortality.^{151,177–179}

It should be mentioned that, except for fatty ocean fish, there is very little vitamin D in commonly consumed natural (ie, not artificially fortified) foods.¹⁷⁷ As such, sensible sun exposure (adjusted to skin type, climate, time of year, and geographic region) and/or supplementation with vitamin D may often be pertinent in order to maintain serum 25[OH]D above 30 ng/mL¹⁷⁷ (or preferably above 45 ng/mL).¹⁷⁹

Another important lifestyle change is physical inactivity, which Booth et al¹⁴⁶ call “an ancient enemy”. They make a compelling case for its possible causal role in insulin resistance, dyslipidemia, obesity, hypertension, type 2 diabetes, coronary artery disease, angina, myocardial infarction, congestive heart failure, stroke, intermittent claudication, gallstones, various types of cancer, age-related cognitive dysfunction, sarcopenia, and osteopenia, among other diseases.

Regarding dietary changes, it should be mentioned that, in the US, dairy products, cereal grains (especially the refined form), refined sugars, refined vegetable oils, and alcohol make up to 70% of the total daily energy consumed.⁶⁵ As pointed out by Cordain et al,⁶⁵ these types of foods would have contributed little or none of the energy in the typical preagricultural hominin diet. These modern foods introduced during the Neolithic, Industrial, and Modern eras have adversely affected the following nutritional characteristics.

Micronutrient density

Calorie per calorie, fish, shellfish, meat, vegetables, and fruit present a higher micronutrient density than does milk (with the exception of calcium) and whole cereal grains (and several orders of magnitude higher than refined grains).⁶⁵ Moreover, vegetable oils and refined sugars represent more than 36% of the energy in a typical US diet and are essentially devoid of micronutrients (except for vitamin E in some vegetable oils).⁶⁵

Therefore, current food choices,^{65,154,180,181} together with soil depletion^{182–186} and modern food transport and

stocking,^{187–189} are perhaps the main reasons why a significant percentage of the North American population does not reach the recommended daily allowance (RDA) of various vitamins and minerals.^{190,191} This problem is exacerbated by culinary methods,^{192–197} smoking (which causes vitamin C depletion¹⁹⁸), and the use of certain foods as staples. For instance, using cereal grains as staple foods may compromise the status of various nutrients, such as vitamin B6 (because of low bioavailability¹⁵⁴), biotin (perhaps because of antinutrients eliciting a depression of biotin metabolism¹⁵⁴), magnesium, calcium, iron, and zinc (because their phytate content reduces intestinal absorption of these minerals^{154,180}).

Even moderate micronutrient deficiency leads to a wide spectrum of pathophysiological events, and it is an important risk factor for several chronic degenerative diseases.^{65,199–206} For instance, data from the National Health and Nutrition Examination Survey 2001–2002 show that magnesium intake for more than 50% of US adults was below the estimated average requirement.¹⁹⁰ Multiple epidemiologic studies associate magnesium deficiency with an increased risk of metabolic syndrome^{201,202} and CVD,^{203–205} and this causal relationship is supported by intervention studies.^{206–209}

Other nutrients whose status is compromised in a typical western diet are zinc, folate, and vitamins C, E, and K,^{190,199,200} the latter (especially the K2 form) gaining widespread acceptance as a possible player in CVD. Epidemiological studies associate higher vitamin K2 intake with a reduced CHD and coronary calcification incidence.^{210–212}

Folic acid deficiency (which would not constitute a problem in hunter–gatherer diets that included green leafy vegetables and organ meats⁶⁵) is also a case for concern in terms of CVD prevention, as it leads to an increase in plasma homocysteine, which, although no consensus has been reached, appears to be a CVD risk factor because it induces damage of the endothelial cell wall and abnormal arterial lipid deposition, reduces vasorelaxation, and impairs fibrinolytic action.²¹³ Perhaps more important, folate, along with vitamin B6 and B12, choline, betaine, and methionine deficiency in utero, may result in an altered epigenetic programming,⁶² which ultimately leads to endothelial dysfunction,²¹⁴ among other pathophysiological consequences.^{62,213}

Sodium/potassium ratio

The average potassium content (2620 mg/d) of the typical US diet is substantially lower than its sodium content (3271 mg/d), which is due to the use of table salt, a high intake of processed foods (with added salt), and the displacement of potassium-rich foods (eg, fruit and vegetables) by

potassium-poor foods, such as vegetable oils, refined sugars, whole grains, and dairy products.⁶⁵

This inversion of potassium and sodium concentrations is a recent event in human evolutionary history.^{63–65,215} It is believed to contribute to hypertension, stroke, kidney stones, osteoporosis, gastrointestinal tract cancers, asthma, exercise-induced asthma, insomnia, air sickness, high-altitude sickness, and Meniere's syndrome.⁶⁵

Net acid load

After digestion, absorption, and metabolism, nearly all foods release either acid or base into the systemic circulation. Dairy products (especially hard cheeses), cereal grains, salt (because of the chloride ion), meats, fish, shellfish, and eggs are net acid yielding, whereas fresh fruit, vegetables, tubers, roots, and nuts are net base yielding.^{65,215}

It was recently estimated that the diet of East African *Homo sapiens* during the Paleolithic era was predominantly net base producing,²¹⁶ as opposed to the typical western diet, which is net acid yielding^{65,215} and hence leads to a chronic, low-grade metabolic acidosis, which elicits loss of calcium ions caused by mobilization of alkaline salts from bone to titrate some of the retained hydrogen ions.²¹⁵ This calcium is lost in the urine without a compensatory increase in gastrointestinal absorption.²¹⁵ Chronic, low-grade metabolic acidosis also induces the release of amino acids, including glutamine and amino acids that the liver can convert to glutamine.²¹⁵ Glutamine is the major nitrogen source used by the kidney for synthesis of ammonia, thereby increasing the excretion of acid (as ammonium ion) in the urine and mitigating the severity of the acidosis.²¹⁵ Accordingly, in the long term, a net acid-yielding diet may increase the risk for osteoporosis and sarcopenia.^{65,215}

Furthermore, a net acid-yielding diet increases not only calcium excretion²¹⁷ but also magnesium excretion.²¹⁸ Finally, there is evidence that chloride (a key determinant of the diet's net acid load²¹⁹) may be a major cause of salt-induced hypertension.²¹⁵

On a final note, this chronic, low-grade metabolic acidosis is exacerbated in elderly people who experience a decline in glomerular filtration rate and hence have a decreased renal acid excretion capacity,⁶⁵ which is why correcting diet-induced chronic metabolic acidosis in this age group is even more important. Hence, we propose as a solution to this chronic, low-grade metabolic acidosis a decreased intake of sodium chloride and an increased consumption of unprocessed fruit and vegetables, at the expense of refined vegetable oils, refined sugars, cereal grains, hard cheeses, and processed foods.

Antinutrient content and inflammatory potential

Alterations in gut microbiota²²⁰ and increased intestinal permeability²²¹ are possible causes of low-grade chronic inflammation. Indeed, when the intestinal barrier is disrupted, it allows increased passage of gut luminal antigens derived from food, bacteria, and viruses²²¹ into peripheral circulation (endotoxemia²²²). One particular antigen, lipopolysaccharide (LPS), from Gram-negative bacteria, is routinely used in animal experiments to induce acute immune stimulation.²²³ When LPS binds Toll-like receptor (TLR)4, it triggers the release of nuclear factor kappa-B (NF- κ B) dimers that translocate into the cell nucleus, where they bind to DNA target sites, thereby inducing the expression of genes that code for various inflammatory enzymes, cytokines and chemokines, cell adhesion molecules, antiapoptotic and angiogenesis proteins, inducible nitric oxide synthase, and matrix-degrading enzymes²²⁴ that are involved in the atherosclerosis process.^{19,166,222,224} Moreover, these proinflammatory cytokines may disrupt insulin signaling, promoting insulin resistance.¹⁶⁴ So a chronic low-grade endotoxemia may lead to low-grade chronic inflammation,²²² which is at the root of various disorders.^{160,165–167,222,224,225}

In this regard, recent evidence shows that certain western foods (dairy cream, butter, egg muffins, sausage muffins, hash browns, and sugar) allow increased passage of luminal antigens into peripheral circulation, leading to TLR2 and TLR4 activation.^{222,226–228} Interestingly, one study found that these events were prevented by a high intake of orange juice (perhaps because it contains flavonoids with reactive oxygen species [ROS] and inflammation-suppressive activities, such as naringenin and hesperidin),²²⁸ which opens the possibility that other fruit and vegetables may elicit similar effects.

Some factors contributing to increased intestinal permeability include nonsteroidal anti-inflammatory drugs,²²¹ antacids,²²¹ changes in gut microbiota,²²¹ alcohol,²²⁹ lectins,²²¹ saponins,^{230–235} and gliadin.²³⁶

It was recently found that gliadin, a prolamine in wheat (which is a novel food in the human diet in evolutionary terms⁶⁵), increases gut permeability by means of zonulin production in the gut enterocytes.²³⁶ Zonulin causes disruption of the tight junction proteins that maintain the gut barrier function and leads to increased gut permeability.²³⁷ In addition, gliadin (which is resistant to heat and digestive enzymes¹⁵⁴) is able to interact with gut-associated lymphoid tissue, stimulating the innate immune system in celiac and nonceliac individuals (whereas the adaptive immune response is exclusive of celiac patients).^{238,239} Gliadin may increase

intestinal permeability and hence induce the production of proinflammatory cytokines, independent of one's genetic predisposition to celiac disease (although, as expected, these effects are more marked in celiac disease).^{236,238–240} As such, we can deduce that chronic consumption of wheat, as happens in western countries, may lead to low-grade chronic inflammation. Of relevance, wheat gluten has been implicated in multiple sclerosis,^{154,241,242} type 1 diabetes,^{154,243} psoriasis,²⁴⁴ immunoglobulin (Ig)A nephropathy,¹⁵⁴ and rheumatoid arthritis (RA).^{154,221} Moreover, rectal mucosal inflammatory response after gluten challenge has been observed in patients with Sjögren's syndrome.²⁴⁵ Furthermore, a gluten-free vegan diet over 1 year significantly reduced disease activity and oxidized low-density lipoprotein cholesterol (LDL-C) in RA patients while raising natural atheroprotective antibodies against phosphorylcholine (anti-PC IgM).²⁴⁶ This may be relevant, as anti-PC IgM is negatively associated with atherosclerosis development in hypertensive individuals,²⁴⁷ and low levels of anti-PC IgM independently predict development of CVD.²⁴⁷ Interestingly, compared with in healthy Swedes, anti-PC IgM has been found to be significantly higher in the horticulturalists of Kitava,²⁴⁸ who, at the time of measurement, followed a diet composed of fish, coconut, fruit, and tubers (and hence devoid of cereal grains, dairy products, separated fats, and sugars)²⁴⁸ and were virtually free of autoimmune diseases, osteoporosis, obesity, insulin resistance and type 2 diabetes, CVD, and acne.^{26,74,82,112,119}

Similar to gliadin, many plant lectins are also a recent introduction to the human diet.¹⁵⁴ Lectins are omnipresent proteins found in the plant kingdom and likely evolved as toxic defensive mechanisms to ward off predators.¹⁰⁰ Most of these glycoproteins are believed to be benign and nontoxic to humans, but the ones that can bind gut tissue may be problematic, such as those found in cereal grains, legumes, and certain solanaceous plants (tomatoes and potatoes).^{154,221,249} Most plant lectins are relatively resistant to heat¹⁵⁴ (unless cooked by pressure cooking²⁵⁰) and digestive enzymes^{154,221} and have been found intact in the gastrointestinal tracts of both animals and humans.^{154,221} Furthermore, in animal models, lectins from legumes and cereal grains disrupt intestinal barrier and immunological function when they bind surface glycans on gut epithelial cells, causing cellular disruption and increasing gut permeability.²²¹ They may also facilitate the growth of Gram-negative bacteria strains,²²¹ which could, in theory, contribute to endotoxemia²²¹ and hence low-grade inflammation through TLR4 activation by LPS.²²² Perhaps even more importantly, wheat germ agglutinin (WGA) (a lectin in wheat) and phytohemagglutinin (PHA) (a lectin

found in beans) are rapidly transported across the gut wall into systemic circulation of animals,²²¹ and tomato and peanut lectins have been found in systemic circulation in humans following consumption of tomato juice and roasted peanuts, respectively.^{249,251}

These findings might be important, as virtually every cell in the body and every extracellular substance can be bound by lectins because of their ability to bind glycosylated structures.¹⁵⁴ Of note, *in vitro* data have shown that WGA can bind insulin and leptin receptors,^{154,252} which could theoretically elicit insulin and leptin resistance.^{26,100,154} Moreover, lectins from lentils, kidney beans, peas, and wheat potently increase the production of inflammatory cytokines (interleukin [IL]-12, IL-2, and interferon γ) in cell cultures,²⁵³ and WGA also stimulates production of tumor necrosis factor (TNF)- α and IL-1 β *in vitro*.²⁵⁴ Furthermore, WGA and PHA induce the production of metalloproteinases (MMPs) in leukocytes,^{255,256} and WGA directly causes the activation of platelets and potently increases their aggregation.²⁵⁷ This may be relevant because rupture of the fibrous cap and formation of the blood clot, which is mediated by MMPs and platelets, is a crucial mechanism involved in thrombus production. In this regard and although these chain of events have not to our knowledge been examined *in vivo*, it should be mentioned that peanut oil has unexpectedly been shown to be highly atherogenic in rats, rabbits, and primates,²⁵⁸ and reduction of its lectin content decreases its atherogenicity.²⁵⁸ Interestingly, one of the very few human-controlled dietary intervention trials with hard endpoints, DART (Diet And Reinfarction Trial), found a tendency toward increased cardiovascular mortality in the group advised to eat more fiber, the majority of which was derived from cereal grains.²⁵⁹ Of relevance is that this nonsignificant effect became statistically significant after adjustment for possible confounding factors (such as medication and health state).²⁶⁰

Another class of antinutrients that may increase intestinal permeability in humans and hence endotoxemia are saponins, which are present in some cereal grains, legumes, quillaja, alfalfa sprouts, and solanaceous plants such as potatoes and green tomatoes.^{230–235} These steroid glycosides or triterpenoids are formed by a sugar compound (glucuronic acid, glucose, or galactose, among others) and an aglycone (nonsugar molecule) portion.^{230,231} By binding the cholesterol molecule on gut cell membranes, the aglycone portion disrupts the gut barrier and increases intestinal permeability.²³¹

Unfortunately, the effects of lectins and saponins on intestinal permeability, endotoxemia, and inflammation have

been poorly studied in humans to allow us to draw significant conclusions.

Novel food processing procedures, such as extreme heating, irradiation, ionization, pasteurization, and sterilization, may also promote low-grade chronic inflammation by leading to the nonenzymatic glycation and oxidation of proteins and lipids in common consumed foods.²⁶¹ This complex and heterogeneous group of compounds, called advanced glycation end products (AGEs) and advanced lipid oxidation end products (ALEs), once partially absorbed into the systemic circulation may have deleterious health effects²⁶¹ by direct modification of proteins and lipids^{262,263} (such as LDL glycation and oxidation, for instance) and perhaps also indirectly via the receptor for AGEs (RAGE).^{261,262} Of relevance to chronic degenerative diseases is the possible interaction of AGEs and ALEs with RAGE, which may activate several intracellular signal transduction pathways that lead to various downstream events, such as the activation of NF- κ B and activator protein-1 transcription factors,^{261,262} which increases the expression of endothelin-1, angiotensin II, adhesion molecules, inflammatory cytokines, and plasmin activator inhibitor-1.^{261,262}

Indeed, in diabetic patients, a high AGE intake was associated with higher levels of C-reactive protein (CRP), TNF- α , and vascular cell adhesion molecule (VCAM-1).²⁶¹ In contrast, low-AGE diets reduce serum AGE levels, as well as markers of inflammation and vascular dysfunction (CRP, TNF- α , and VCAM-1) in diabetic and renal failure patients.^{261,262} The effects of dietary AGEs and ALEs are obviously more pronounced in diabetics (who present an enhanced formation of endogenous AGEs due to hyperglycemia)²⁶¹ and kidney failure patients (who have an impairment of AGE renal excretion).²⁶¹ Nevertheless, in a cross-sectional study of healthy subjects of different ages, dietary AGE intake was an independent determinant of high-sensitivity CRP and of circulating AGEs, which, in turn, were associated with endogenous lipid peroxidation and HOMA index.²⁶³

AGE and ALE content in food is greatly influenced by processing and cooking conditions, including temperature, time, and moisture.²⁶⁴ Consequently, the avoidance of processed foods and the use of steaming, poaching, boiling, and stewing as the main cooking methods, instead of frying, broiling, and grilling, may be a sensible way to decrease the formation of these compounds.^{261,264} Of interest, tobacco, by being processed in the presence of reducing sugars, represents another source of exogenous AGEs.²⁶² Indeed, circulating AGE levels have been found to be significantly higher in smokers than in nonsmokers.²⁶⁵

Glycemic load, fiber, and fructose

During the Paleolithic period, most of the carbohydrate (CHO) sources were wild fruit, berries, vegetables (typically presenting low glycemic index [GI]²⁶), and sometimes tubers, with cereal and honey intake being scarce.^{14,26,65}

Today, most CHO come from processed foods such as refined sugars and refined cereal grains.⁶⁵ Even whole grains possess a higher glycemic load (GL) than does most unprocessed fruit and vegetables.⁶⁵ The GL takes into account both the GI and the amount of CHO in a given serving of a food. It is estimated that the GL of Paleolithic diets was significantly lower than the GL of western diets.⁶⁵

This observation is relevant because chronic adoption of a high-GL diet may lead to hyperglycemia and hyperinsulinemia,²⁶⁶ which may contribute to dyslipidemia (elevated serum triglycerides, small-dense LDL-C, and reduced high-density lipoprotein [HDL]-C),²⁶⁶ hypertension,²⁶⁷ elevated plasma uric acid,²⁶⁷ and insulin resistance,²⁶⁶ the primary metabolic defect in metabolic syndrome.²⁶⁶ Moreover, by eliciting postprandial hyperglycemia, it may increase oxidative stress, proinflammatory cytokines, protein glycation, and procoagulant activity, thereby adversely affecting endothelial function, among other pathophysiological effects.^{266,268–270} Indeed, a recent meta-analysis of 37 prospective cohort studies suggests that diets with a high GI, high GL, or both may increase the risk of type 2 diabetes, heart disease, and gallbladder disease.²⁷⁰ Furthermore, intervention studies show that a low GL diet may be an effective strategy for overweight and obesity^{271,272} and confer better glucose, insulin, lipoprotein, and inflammatory cytokine profiles in overweight and type 2 diabetes patients.²⁶⁸ Finally, the chronic adoption of a high GL diet may lead to a number of hormonal changes (such as elevated insulin-like growth factor-1 [IGF-1]/insulin-like growth factor binding protein-3 [IGFBP-3] ratio and increased ovarian and testicular androgen synthesis, coupled with decreased sex hormone-binding globulin hepatic synthesis) that ultimately may result in polycystic ovary syndrome, epithelial cell cancers, acne, and juvenile myopia, among other diseases.^{85,119,266,273}

Another nutritional change is fiber intake. Most Paleolithic diets had more fiber (>30 g/d), generally from fruit and vegetables,⁶⁵ than did the typical western diet, where most of the fiber derives from cereal grains.⁶⁵ Fruit and vegetables have, on a calorie per calorie basis, two and eight times more fiber than do whole grains.⁶⁵ In addition, fruit and vegetables typically contain soluble fiber, whereas much fiber in cereal grains is of the insoluble type.²⁶

This may all be relevant because dietary fiber, in particular soluble fiber, increases satiety,^{274,275} reduces postprandial free fatty acids,²⁷⁵ and contributes to better glycemic control (perhaps through a glucagon-like peptide-1 effect).²⁷⁵ Furthermore, dietary fiber appears to play an important role in intestinal health, as suggested by Higginson and Oettlé²⁷⁶ in the 1960s. They observed that in Africa, where “a large amount of roughage is consumed”, colon cancer and constipation were rare, whereas they were common diseases in western countries. This was also observed by Calder et al,²⁷⁷ who reported that a shift from rural to urban living and at the same time from a traditional to a western diet (containing a low amount of fiber) and lifestyle in Kenya was associated with diverticulitis and colon carcinoma. Today, there is an increasing recognition and understanding of the complex role that fiber plays in maintaining intestinal health that goes beyond the “traditional” increased bulk and stool frequency effect. For instance, dietary fiber fermentation in human intestine produces short-chain fatty acids, mainly acetic acid, propionic acid, and butyric acid,²⁷⁸ which exert several beneficial effects on the intestinal tract. For instance, butyrate and propionate, by inhibition of histone deacetylase, are able to block the generation of dendritic cells (DCs) from bone marrow stem cells, thereby inhibiting the inflammatory response mediated by DCs.²⁷⁹ Also, butyrate controls the assembly of epithelial cell tight junctions, leading to decreased intestinal permeability,²⁸⁰ which may be central to many inflammatory diseases, as explained previously. Even more relevant, butyrate reduces bacterial translocation into peripheral circulation independently of intestinal permeability,²⁸¹ most likely through decreased NF- κ B activation.²⁸¹

Although whole grains are increasingly being recommended, in part to increase fiber intake, given its potential adverse effects already discussed, it would perhaps be prudent that most of the dietary fiber came from fruit and vegetables.

Perhaps even more important, the introduction of refined sugars and, more recently, of high fructose corn syrup (HFCS), has increased fructose intake to unprecedented high levels.^{65,135} Mounting evidence suggests that this dietary shift may be an important player in obesity, insulin resistance, dyslipidemia, gout, hypertension, kidney disease, and nonalcoholic fatty liver disease.^{65,135,266,282,283} Although fruit is a natural source of fructose, it also contains vitamin C, which offsets some of the adverse effects of fructose,¹³⁵ and various other nutrients, as well as fiber. As such, consuming unprocessed

fruit is not equivalent to consuming pure fructose, sucrose, or HFCS.

The simple fact that fructose presents a low GI,²⁶⁶ but yet because of its unique metabolism^{135,266} may have numerous adverse effects, combined with the fact that cereal grains and isolated sugars are the primary high-GL foods in the western diet,⁶⁵ suggests that the historical focus on the GI and GL is incomplete and has to account for fructose and, perhaps more important, the food source of CHO.

Another food group that was not part of Paleolithic diets but is considered a staple today is dairy.⁶⁵ Milk, yoghurt, and some lactose-containing cheeses, despite having a low GL, elicit a very high insulin response.^{284–288} The implications of these findings are not entirely known, because the epidemiological evidence is conflicting regarding the association of milk and dairy, insulin resistance, and metabolic syndrome,^{289–294} but a small dietary intervention study in young boys observed an increase of 103% and 75% in fasting plasma insulin concentrations and relative insulin resistance, respectively, after 7 days on a high-milk diet.²⁸⁸ Furthermore, epidemiologic and intervention studies in children and adults demonstrate that cow's milk significantly increases plasma levels of IGF-1 and, perhaps more important, the IGF-1/IGFBP-3 ratio.²⁹⁵ Moreover, milk contains various hormones and growth factors^{296–300} that may have relevant implications for chronic degenerative diseases. Indeed, epidemiologic evidence suggests that milk may be implicated in acne^{273,300} and epithelial cell cancers,²⁹⁵ particularly prostate cancer.³⁰⁰ Most of these adverse effects are more likely to manifest in the postreproductive years and, as such, would not negatively affect the selection of ALP-associated alleles. Indeed, as indicated previously, genes that are important for early reproductive success can be selected despite potentially detrimental effects subsequent to their continued expression in later life,³⁰¹ which is why ALP should not be viewed as genetic protection against potential adverse effects derived from long-term dairy intake.

It should be mentioned that reactive monosaccharides such as glucose and especially galactose (from dairy)³⁰² and fructose³⁰³ (which are much more reactive than glucose)^{302,303} lead to AGE production and accumulate intra- and extracellularly.³⁰³ Moreover, chronic hyperglycemia is a well-known accelerator of endogenous AGE production.²⁶¹ In this regard, the chronic consumption of a high intake of sucrose, fructose, and galactose and/or the adoption of a high GL diet may significantly contribute to the formation of AGEs.

It can therefore be concluded that an increase in diet's GL and insulinotropic potential, coupled with a higher fructose (and possibly galactose) intake and a reduction in vitamin C and dietary fiber consumption, may be another cause of the high incidence and prevalence in industrialized countries of epithelial cell cancers, obesity, metabolic syndrome, gout, CHD, acne, myopia, and various gastrointestinal problems, including constipation, irritable bowel syndrome, and diverticulitis.

Macronutrient distribution

The percentage of total food energy (en%) derived from macronutrients in Paleolithic diets would typically be different from current official dietary guidelines (protein = 15 en%; CHO = 55–60 en%, and dietary fat ≤ 30 en%).⁶⁵ Cordain et al¹⁵⁵ estimated that the diets of historically studied hunter-gatherer populations were higher in protein (19–35 en%), lower in CHO (22–40 en%), and equivalent or even higher in dietary fat (28–58 en%).

Even though the RDA for daily protein is 0.8 g/kg of bodyweight,³⁰⁴ there is evidence that athletes need higher amounts (in sports medicine, protein intake of 1.4–2 g/kg/d is increasingly being recommended³⁰⁵). The elderly also need a higher protein intake to prevent or attenuate sarcopenia³⁰⁶ and osteopenia,^{307–309} because dietary protein increases calcium absorption^{307,308} and has an anabolic effect on muscle^{305,306} and bone cells^{309,310} (especially in the context of a net base-yielding diet³¹⁰). Moreover, high-protein diets (>20% of caloric intake⁶⁵) have been shown to improve dyslipidemia^{65,108,109} and insulin sensitivity^{65,81,108} and are potential effective strategies for improving obesity,^{65,271,311} metabolic syndrome,⁶⁵ and hypertension.^{65,312} Furthermore, a long-term high-protein intake does not appear to adversely affect renal function in individuals without pre-existing kidney disease.^{313–316} Nevertheless, there is a hepatic urea synthesis limit, which lies between 2.6 g/kg/d and 3.6 g/kg/d.¹⁵⁵

Regarding the lower CHO content of preagricultural diets, it should be mentioned that mounting evidence suggests that a reduced-CHO diet may be superior to a western-type low-fat, high-CHO diet, especially in metabolic syndrome patients, because it may lead to better improvement in insulin resistance, postprandial lipemia, serum triglycerides, HDL-C, total cholesterol/HDL-C (TC/HDL-C) ratio, LDL particle distribution, apolipoprotein (apo)B/apo A-1 ratio, postprandial vascular function, and certain inflammatory biomarkers (such as TNF- α , IL-6, IL-8, MCP-1, E-selectin, ICAM, and PAI-1).^{317,318} Nevertheless, because a low-CHO

diet is obviously lower in sugars (such as sucrose and fructose) and cereal grains and is often higher in protein, it is unlikely that all of its positive effects can be attributed solely to CHO restriction.

The concern that adopting a preagriculture-type diet may encourage a higher intake of dietary fat with a consequent increase in CVD risk is not justifiable, because the absolute amount of dietary fat consumed is probably much less important than is the type of fat consumed.^{24,108,319} For instance, the traditional diet of Crete, which served as a guiding template for the “Mediterranean Diet” used in clinical trials, had 35–40 en% from fat (especially *cis* monounsaturated fatty acids [*cis* MUFA] from olive oil and *cis* polyunsaturated fatty acids [*cis* PUFA] of the omega-3 family, supplied by fish, egg yolk, and wild plants such as purslane).³¹⁹ The death rates from cancer and heart disease in this region of Greece were one-third the corresponding death rates in the US.³¹⁹

Indeed, Mediterranean populations consuming diets rich in *cis* MUFA from virgin olive oil have lower CHD rates,³¹⁹ and in a recent reconstructed East African Paleolithic diet,¹⁵⁷ MUFA represented 6–19 en%. Furthermore, various observational studies have reported an inverse association between *cis* MUFA and CHD risk.²⁴ Moreover, *cis* MUFA intake is associated with improved lipoprotein parameters, reduced LDL oxidation, improved insulin sensitivity, and reduced thrombogenesis,²⁴ and when it replaces CHO it decreases triglycerides and total cholesterol/HDL-C ratio.³²⁰

A possible and widely available food source of *cis* MUFA (which in evolutionary terms is a novel but yet apparently beneficial food) is virgin olive oil^{321,322} that also contains vitamin E (especially α -, β -, and γ -tocopherol) and phenolic compounds, which may reduce LDL and DNA oxidation and increase plasma antioxidant capacity, resulting in less vascular damage by ROS.^{321,322} Furthermore, it may decrease the activation of NF- κ B, inhibit endothelial adhesion molecule expression and platelet aggregation, and increase nitric oxide availability.^{321,322}

In the reconstructed East African Paleolithic diet¹⁵⁷ mentioned previously, the intake of saturated fatty acids (SAFA) was estimated at 11–12 en%, and Cordain¹⁵⁶ approximated that in historically studied hunter–gatherer populations around the globe, SAFA comprised 10–15 en%. Although this is higher than the recommended intake ($\leq 10\%$),⁶⁵ it should be mentioned that even a 10 en% increase in SAFA intake replacing complex CHO is estimated to raise total and LDL-C by only 20 mg/dL and 15 mg/dL (0.005 mmol/L and 0.004 mmol/L), respectively.³²³ In addition, replacement of SAFA by refined CHO and sugars increases triglyceride levels and small LDL

particles and reduces HDL-C.^{320,324} Moreover, not all SAFA behave in the same manner. For instance, lauric acid has a more favourable effect on TC/HDL-C than does CHO and any other fatty acid, either saturated or unsaturated,³²⁰ whereas myristic and palmitic acids appear to have little effect on this CHD risk factor.³²⁰ Furthermore, a recent meta-analysis does not support the notion that SAFA increase the risk of CHD, stroke, or CVD,³²⁵ and replacement of SAFA with high GI CHO has actually been found to significantly increase the risk of myocardial infarction in a recent prospective cohort study including 53,664 women and men.³²⁶ Also, there are populations, such as the horticulturalists of Kitava and the natives of Tokelau (Pacific Island), with very high SAFA intake from coconut (up to 45% of total energy in the case of Tokelau³²⁷) and apparently low CHD rates.^{68,112,327}

Finally, SAFA, when consumed in the context of a higher-protein, reduced-CHO diet, are not metabolically equivalent to SAFA in the context of the typical western diet or even in the context of a prudent low-fat, high-CHO diet. Indeed, a recent trial observed that a reduced-CHO diet led to a significant decrease in circulating SAFA in triacylglycerols and cholesteryl ester, compared to a low-fat, high-CHO diet containing 3 times less dietary SAFA.³²⁸

In light of that information, we propose increasing the intake of protein (in the form of fish, shellfish, meat from grass-fed and game animals, and eggs from free-range hens) and *cis* MUFA (through virgin olive oil, avocados, and nuts), decreasing CHO consumption (especially separated sugars and cereal grains), and maintaining a moderate intake of SAFA. We also support an elimination of industrial trans fatty acids (TFA), which have no precedent in human history and are a recognized CHD risk factor,^{24,65} and perhaps replacing myristic and palmitic acids with lauric acid. This can be achieved through avoidance of fatty domesticated meats and dairy products and moderate consumption of virgin coconut oil, which presents antimicrobial properties,¹⁵⁷ may promote a more pronounced reduction in abdominal obesity in the context of a hypocaloric diet,³²⁹ and may also decrease TC/HDL-C,³²⁰ LDL oxidation,³³⁰ and lipoprotein(a).³³¹

Omega-6/omega-3 ratio

Kuipers et al¹⁵⁷ estimated a total *cis* PUFA intake between 8.6 en% and 15.2 en% in East African Paleolithic diets. But more important is the balance between omega-6 and omega-3 *cis* PUFA. In this regard, the ancestral dietary intake of alpha-linolenic acid (ALA) and linoleic acid (LA) constituted 3.7–4.7 en% and 2.3–3.6 en%, respectively,¹⁵⁷ whereas, in the US,²⁴ ALA represents only 0.6 en% and LA 6–7 en%,

with similar intake having been reported in various western countries, leading to an unprecedented increase in the LA/ALA ratio of the western diet^{13,65} to >10/1, mainly due to widespread use of LA-rich vegetable oils.^{14,24,26,65,157}

This practice may have important implications, because a high LA/ALA ratio is found in countries with a high CHD incidence,^{332,333} and a high LA intake reduces the omega-3 index³³⁴ (defined as the percentage of eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA] in red blood cell membranes, relative to all other fatty acids), which has been proposed as a new CHD risk factor.³³⁵ Moreover, as reviewed by Calder,³³⁶ *in vitro* data from human endothelial cell studies demonstrate that LA activates NF- κ B, leading to a subsequent production of proinflammatory cytokines such as IL-6 and TNF- α .

More important, the long-held notion that replacing SAFA with LA will reduce CHD risk has recently been challenged.³³⁷ As reviewed by Ramsden et al,³³⁷ only when SAFA and TFA were replaced by a combination of omega-6 and omega-3 *cis* PUFA was there a reduced risk of CHD in randomized controlled trials. In fact, LA-specific diets actually produced nonsignificant trends toward increased risks of all CHD endpoints in randomized controlled trials, with the increased risk of death from any cause approaching statistical significance.³³⁷ This data, coupled with a long-term multiple intervention trial with a diet of reduced omega-6 fatty acids and increased omega-3 fatty acids, which showed a 70% reduction in CHD events and mortality,³³⁸ strongly suggest that a high LA intake is not necessary to decrease CHD risk and may possibly increase it.

As for long-chain PUFA, Kuipers et al¹⁵⁷ estimated that the intake of omega-3 fatty acids (EPA + DHA) and omega-6 arachidonic acid (AA) in East African Paleolithic diets was 1.7–14.2 g/d and 1.81–5.46 g/d, respectively. This figure contrasts with an EPA + DHA and AA mean intake of 0.11 g/d and 0.2 g/d, respectively, in the western diet.^{24,157}

If the omega-3 index becomes accepted as a CHD risk factor, then a reduced intake of omega-3 fatty acids (EPA + DHA) in the western diet is cause for serious concern. This observation is further supported by data showing that increased consumption of omega-3 fatty acids reduces the risk of cardiovascular mortality in both epidemiological and intervention studies.^{24,65} Many of these effects may derive from the fact that these fatty acids reduce ventricular arrhythmias²⁴ and are naturally ligands for peroxisome proliferator-activated receptors (PPAR), sterol regulatory element-binding proteins (SREBP), and carbohydrate responsive element-binding protein (ChREBP).³³⁹ Hence, these fatty

acids modulate gene expression involved in lipid metabolism, lipogenesis, fatty acid oxidation, cholesterol metabolism, adipokine secretion, glucose metabolism, insulin sensitivity, and inflammation.³³⁹ Furthermore, they directly downregulate the transcription factor NF- κ B, which has a major role in the induction of proinflammatory genes.³³⁹

On a final note, it should be mentioned that although a Paleolithic-type diet would lead to a higher intake of AA and AA-derived eicosanoids, which initiate inflammation, AA also produces lipoxins that, together with resolvins from EPA and DHA and protectins and maresins from DHA, are involved in the resolution phase of inflammation.^{339,340} Accordingly, increasing the consumption of omega-3 fatty acids (EPA + DHA) from fatty fish and/or omega-3 supplements, choosing eggs and meats from grass-fed animals (which have a lower omega-6/omega-3 ratio than do grain-fed animal meat and eggs^{108,319}), and decreasing the consumption of LA-rich vegetable oils may be an effective strategy to reduce the risk of various chronic inflammatory diseases.

Conclusion

The adoption of diet and lifestyle that are very different from what shaped the human genome for more than 2 million years is a major factor in the widespread prevalence of chronic degenerative diseases that are epidemic in western countries. This conclusion strongly suggests that focusing on isolated dietary or lifestyle variables is not an appropriate preventive medicine strategy.

Indeed, the evolutionary template predicts that optimal gene expression, and ultimately an increase in health span (the number of years in good health), even if it would not affect average life expectancy, will not be achieved by any single dietary or lifestyle change but rather through the combination of several measures, such as regular physical exercise; stress management; sun exposure according to latitude and skin color (in order to maintain plasma 25[OH] D above 45 ng/mL and at the same time avoiding the adverse effects of excessive sun exposure); adequate sleep; avoidance of tobacco smoke; reduced exposure to pollutants, dietary AGEs, ALES, and other Maillard reaction compounds; and the adoption of a diet similar to that followed by Paleolithic hunter-gatherers. Giving support to this notion, four recent human intervention trials^{18,23,341,342} and one animal trial³⁴³ have demonstrated that a diet composed of meat, fish, shellfish, eggs, fresh fruit and vegetables, roots, tubers, nuts, and seeds may be superior to so-called healthy diets such as the Mediterranean diet.³⁴¹

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