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EVOLUTIONARY MEDICINE view

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SUMÁRIO

ABSTRACT

From the evolutionary theory, the body is not a product of design but a bundle of compromises shaped by natural selection to maximize reproduction or genetic fitness, not health. Hence, life history theory predicts the coordinated evolution of the traits contributing directly to fitness: age and size at maturation, number and size of offspring, number of reproductive events, and ageing and lifespan. Major constraints were famine and infection with the trade-offs of encephalization-gut size; growth-immunological defense and longevity-reproduction. The major functions involved in lifespan are maintenance, growth, reproduction, and defense, in which energy can be invested. For those, insulin resistance, sodium preservation and inflammation are seen as thriftiness in situations such as famine, water privation and infection. For then, emerged the thrifty genotype. An evolutionary view suggests that many genetic variants interact with environments and other genes during development to influence disease phenotypes. Therefore, it is possible to analyze a great number of diseases in terms of adaptive vulnerabilities connected to our phylogenetic inheritance, such as human bodily inadequacies in relation to the modern environment. This means that current diseases such as obesity, T2D, essential hypertension, dyslipidemia and metabolic syndrome may result from the mismatch of our ancestral thrifty genotype with the contemporary way of life through epigenetic modification of the gene expression. Additionally, the worldwide burden of NCDs demands the implementation of effective population-based strategies. This is the basis of the Behavioral Medicine whose major principles are dietary adequacy and physical activity. As a model, we propose an ongoing epidemiological experience ("Moving for Health Program"), described as a costless lifestyle -modification procedure, alternatively to the current homeostatic model adopted by the Public Service. It could be a natural remedy for recovering part of the imbalance caused by modern life-styles, costless and without the side effects of many pharmacological treatments.

KEYWORDS: Evolutionary Biology and Medicine; Epigenetics of Non-communicable Chronic Diseases; Behavioral Medicine.

SYNOPSIS

1 | BACKGROUND

Chronic diseases are the foremost cause of death globally and this prevalence continues to rise for both men and women, every ethnicity, and all age groups (1). Non-Communicable Diseases (NCDs) are defined as a disease that is slow in its progress and long in its continuance (2). Major examples of NCDs are cardiovascular diseases (including hypertension atherosclerosis, coronary heart disease heart failure, and stroke), obesity, Type 2 diabetes (T2D), some cancers, allergy, osteoporosis, sarcopenia (and frailty), neurodegeneration, cognitive failure and depression. Besides its organic or mental failure, NCDs affect also patient's autonomy for daily living activities which can be evaluated by the 'Disability-Adjusted Life Years (DALYS) (2).

The Brazilian Universal Health System (SUS) is committed to offer high-quality health care to the entire population, including the distribution free of charge of a list of essential medicines aimed at treating the most prevalent diseases in the population (3). The expansion of pharmaceutical care and the free distribution of most NCD medications by SUS, play an important role in the Brazilian Government's effort to tackle NCDs (4). However, NCD medications are expensive. In the first decade of this century (2002-2006), the prescription drug costs was the increasingly large component of overall health care costs of the Brazilian Ministry of Health, varying from 5.4% to 11% of total expenditure. Overall, the increased expenditure with drugs varied from 16.36% in 2002 to 49.7% in 2003 and 45.85% in 2005, summing up 123.9% (2002-2006) (5).

While Brazil's national drug policy calls for distribution of essential drugs through the universal public health system, the stocking of these drugs in outpatient facilities is still deficient. Consequently, the drug access through the SUS is still insufficient lacking of affordability and availability creating socioeconomic inequities by the access to public drugs. The state of out-of pocket added to the much higher prices of medical drugs in Brazil than internationally, is leading the general population to the catastrophic expenditure in health. Hence, despite its accomplishments, the Brazilian health system faces serious financial and organizational challenges. Thus, besides drug therapy is used worldwide as measure in halting and reversing the NCDs epidemic, in Brazil, the burden of NCDs has demonstrated the onerous expansion of pharmaceutical care and the free distribution of most NCD's medications, as an ineffective action in controlling these diseases (2).

Underlying why drug therapy has been largely unsuccessful in halting and reversing the NCDs epidemic, would be the ineffectiveness of the treatment approach by homeostasis model (6). Homeostasis describes mechanisms that hold constant a controlled variable by sensing its deviation from a "setpoint" and feeding back to correct the error. Based on this model physicians reason that when a parameter deviates from its setpoint value, some

internal mechanism must be broken. Consequently, they design therapies to restore the "inappropriate" value to "normal" (6).

Homeostasis treats low level targets and following the homeostasis model, hypertension is treated with drugs that target the three primary effectors of elevated pressure (diuretics, vasoconstrictor antagonists and heart rate antagonists). For obesity, it is listed six neuromodulators that increase feeding and ten that decrease feeding, and then concludes, "a multi-drug regimen that targets multiple sites within the weight-regulatory system may be necessary to achieve and sustain weight loss in many individuals" (7). The same strategy is proposed for type 2 diabetes and metabolic syndrome (8) and, for drug addictions (9). For sure there are "side-effects" involved in each of the steps and the pharmaceutical industry continues to target myriad molecules that regulate these mechanisms, and fundamental research widely promises to identify new targets (10). For all of these, the high discontinuance rates are considered to reflect, among other factors, "a combination of adverse drug effects, cost of drugs, and poor efficacy" (11). Overall, in medicine, major diseases rise in prevalence, such as essential hypertension and type 2 diabetes, whose causes the homeostasis model cannot explain (10).

2 | OUTLINES

By following homeostasis approach, actual medicine ignores evolution (see main text, item 1), and instead focus upon proximate mechanical causes. As a result of assuming this model, medicine is mechanistic, materialistic, reductionist, linear-causal, and deterministic in its concepts. It seeks explanations for diseases, or their symptoms, signs, and cause in single, materialistic changes within the body wrought directly by infectious, toxic, or traumatic agents (6).

In its ignorance to the evolutionary principles, current medicine remains largely pre-evolutionary, excelling in description and mechanistic explanations, but only beginning to explain the variability in disease susceptibility in individuals and populations (12). By going beyond standard care, an understanding of each individual's ongoing life history could guide personalized decisions concerning the prevention, diagnosis, and treatment of disease.

Evolutionary Medicine (see main text, item 1) aims to explain diseases based both on recent physiological causes, those most commonly addressed by medicine, and on more distant evolutionary causes, those responsible for the emergence and survival of useful and functional biological structures throughout the history of the planet. Far from suggesting quick new cures, the general messages of Evolutionary Medicine help to explain why disease is so prevalent and difficult to prevent. The evolutionary thinking on medical issues can sometimes illuminate features quite unexpected by non-evolutionary approaches (13).

Physicians and public health professionals deal with phenotypes, but according

to evolutionary theory (see main text, item 2), bodies are shaped in small increments to maximize reproduction or genetic fitness, not health. Therefore, bodies are vulnerable to disease, and remarkably resilient. From the evolutionary theory, the body is not a product of design but of natural selection, though Evolutionary Medicine rests on the assumption that functional biological characteristics are the result of evolutionary adaptive processes. Genetic traits may be positively or negatively selected relative to their concordance or discordance with environmental selective pressures. “Bodies are vulnerable to disease, and remarkably resilient, precisely because they are not machines built from a plan” (14). They are, instead, bundles of compromises shaped by natural selection in small increments to maximize reproduction, not health” (14). Consequently, natural selection has not shaped organisms for maximum health, but rather to maximize their reproductive success (or genetic fitness).

For contributing to our main fitness of reproductive success, the life history theory (see Main Text, item 3) was developed to predict the coordinated evolution of the traits contributing directly to fitness: age and size at maturation, number and size of offspring, number of reproductive events, and ageing and lifespan. For achieving those, organisms are full of unavoidable trade-offs and constraints. Trade-offs are features inherited or acquired during development. A trade-off occurs whenever a change in one trait that increases fitness is connected to a change in another trait that decreases fitness. Each individual represents a bundle of many trade-offs. Therefore, the life history theory views the evolution of the fitness traits (larger brains, slower growth, longer-lived offspring) as the product of trade-offs (brain-gut, growth-immunity, fertility-lifespan) and extrinsic factors in the environment that affect mortality risk and resource availability. It then considers how extrinsic factors shape the combination of intrinsic traits to maximize fitness (15). The trait of undernutrition (energy deficiency) reduces not only survival but, anticipates fertility and abbreviates mother’s lifespan.

Life history theory models phenotypic evolution (see item 3.5). For though, plastic responses to environmental stimuli include physiological adaptations implemented by homoeostatic feedback loops that can react in seconds or minutes, acclimations (e.g. adjustments to altitude) that can react in days to weeks through changes in the setpoints of feedback loops, and finally, developmental plasticity, in which reactions usually last a lifetime (16,17). Organisms are bundles of compromises shaped by natural selection and, humans and other primates have evolved particular morphological and biological traits that distinguish them from most other mammals.

Life is the interplay between structure and energy and, the major functions involved in lifespan are maintenance, growth, reproduction, and defense, in which energy can be invested. For then, emerged the thrifty genotype (see item 5) that implies some degree of prosperity deriving from earlier frugality and a careful management of resources (18).

Then, hormones (see item 3.1) and other circulating factors provide cues that allow cellular behavior to be matched to organismal goals. For energy saving and energy-yielding substrate distribution, fat storage and insulin resistance can be seen as thriftiness in situation such as famine (19,20). Similarly, sodium preservation during water privation (21) and inflammation in situations of infection (22).

Since about 100,000 years ago humans have started to spread across the whole world to become the only Homo species currently inhabiting this planet. The "Out-of-Africa" Diaspora (see item 6) necessitated adaptation to new conditions of existence. Changes in physical characteristics gave rise to the concept of "race," which is however better described by "geographical location" of origination as shown by studies of human genetic variation (23). The retreat of sea waters in straits of Gibraltar and Bering allowed ancient human to reach Eurasia and American continents. The coalescent-based analysis revealed strong evidence for distinct demographic expansions in Europe, southeastern Asia, and sub-Saharan Africa within the past 10,000y (24). Besides latitude and longitude distances and climate changes, there were major recognized dietary changes (25). Genetic traits may be positively or negatively selected relative to their concordance or discordance with environmental selective pressures. When environmental conditions permanently change, evolutionary discordance arises between a species' genome and its environment, and stabilizing selection is replaced by directional selection, moving the average population genome to a new set point. Individuals bearing the previous average status quo genome experience evolutionary discordance that manifests itself phenotypically as disease, increased morbidity and mortality, and reduced reproductive success.

Nevertheless, there are also the genetic traits positively selected relative to their concordance (by some of their alleles) with environmental selective pressures. When the environment remains relatively constant, stabilizing selection tends to maintain genetic traits that represent the optimal average for a population. This is the frugal gene theory (see item 7), a genetic characteristics that prove to be advantageous in some way would be maintained in a population through a process of positive selection (26). Samples of positive concordance frugality are depicted by alleles ApoE-4 and mutant ABCA1 of plasma cholesterol and thriftiness of energy economy, inflammation and sodium-dependent water retention. However, an evolutionary view suggests that many genetic variants interact with environments and other genes during development to influence disease phenotypes (see item 7.4). Evolutionary Medicine points out that, because biological evolution is much slower than cultural change, much disease arises from the mismatch of our bodies to modern environments (13). Therefore, it is possible to analyze a great number of diseases in terms of adaptive vulnerabilities connected to our phylogenetic inheritance, such as human bodily inadequacies in relation to the modern environment. In fact, the mismatch of our ancestral thrifty genotype with the contemporary way of life would result in diseases such as obesity,

T2D, essential hypertension, dyslipidemia and metabolic syndrome. The evolution towards to high-quality diet for body growth and encephalization, began with the “meat-adaptive” genes allowing our hominid ancestors to more effectively exploit diets with higher levels of animal fat. Additionally, during feast–famine over tens of thousands of years selected some genotypes and genes to oscillate, some of which might also play a role in efficiency during fuel usage. Evolution selected these genes for glucose storage and conservation. However, the idea that common heritable diseases are caused by a few defective genes is usually incorrect. An evolutionary view suggests that many genetic variants interact with environments and other genes during development to influence disease phenotypes. Then, the modern-day environmental constraints and human behavior generated the frugal gene theory. Epigenetic modification of gene expression is one mechanism by which genetic susceptibility and environmental insults can lead to mostly of the contemporary NCDs. In the nutritional field, nutrients and bioactive food components can modify epigenetic phenomena and alter the expression of genes at the transcriptional level by histone modifications and DNA methylation. Thus, epigenetic modification of gene expression is one mechanism by which genetic susceptibility and environmental insults can lead to mostly of the contemporary NCDs (see item 8).

The interface of evolutionary biology and medicine (see items 2.3.1 and 7.5) understood that “humans coevolved with a normal community of symbiotic and parasitic microorganisms” and, we have learned that pathogens evolve much faster than we do, so infection is unavoidable because pathogens rapidly evolve resistance to antibiotics and, pathogens evolve strategies to circumvent host defenses, and the virulence levels are shaped by natural selection to maximize transmission. Similarly to the evolved resistance of pathogens to antibiotics, cancers rapidly evolve resistance to chemotherapy. Thus, far from suggesting quick new cures, the general messages of Evolutionary Medicine help to explain why disease is so prevalent and difficult to prevent (27).

Today it is clear that lifestyle factors and human health are linked through epigenetics mechanisms (18) therefore, the modern human bodily inadequacies in relation to the modern environment can be associated with either dietary inadequacy and/or physical inactivity (28). Nutritional behavior may modulate overweight by eating high energy-dense food, highly refined carbohydrate (CHO) and fat diet, low- micronutrient diet (29). In the same way, physical inactivity may modulate human physiology by reducing cardiorespiratory fitness (mitochondria biogenesis and beta oxidation) and therefore increasing body fatness through lowering the energy expenditure (30).

3 | FUTURE DIRECTIONS

As homeostasis, allostasis is also an endogenous system responsible for maintaining

the internal stability of the organism. But, differently from homeostasis, constancy is not the goal of allostasis, instead, the core idea of allostasis is a coordinated variation to optimize performance at the least cost. The allostasis model defines health as optimal predictive fluctuation. A system becomes unhealthy when, high demand predominates for long times, The allostasis model of physiological regulation, attributes NCDs diseases to sustained neural signals that arise from unsatisfactory social interactions (6). Differently from treating low level targets by drugs (homeostatic model) and generating iatrogenesis, the allostasis model has a more rational goal of intervention with lifestyle modification of environmental factors. Under this model the hallmark of health is the therapeutics of contemporary chronic diseases through principles of Behavioral Medicine, by changing lifestyle, which seems more clinically effective than drugs (2).

As a model of Behavioral Medicine, we have published a costless lifestyle modification program ('Moving for Health") that alternatively to homeostatic model, has proactively promoted eutrophy and also, reduced blood hypertension, T2D and Metabolic Syndrome (31). This community-based ongoing epidemiological "Moving for Health Program", has been conducted since 1991 and, is in very much tune with the ACSM's "Exercise is Medicine" initiative, and WHO proposal. The effectiveness of this Program in reducing overweight (32), T2D (33), hypertension (34) and Metabolic Syndrome (35), have been shown with its estimated economic impact on NCD care (31).

EVOLUTIONARY MEDICINE

Evolutionary Medicine can be defined as the application of the theory of evolution through natural selection to the understanding of human health problems. Therefore, evolutionary medicine or Darwinian medicine is the application of modern evolutionary theory to understanding health and disease. To date, evolutionary medicine has primarily aimed to go beyond understanding how people become ill by considering why the body is susceptible to disease. In particular, these approaches could improve understanding of the effect of ecological change on health, whether this relates to non-human or societal factors (36).

Evolutionary Medicine rests on the assumption that functional biological characteristics are the result of evolutionary adaptive processes. Therefore, it is possible to analyze a great number of diseases in terms of adaptive vulnerabilities connected to our phylogenetic inheritance, such as human bodily inadequacies in relation to the modern environment. This innovative approach provides the medical field with a theoretical framework which contributes to the explanation of a great variety of serious disorders (37). The opportunities generated by Evolutionary Medicine are large in the clinic, the research laboratory, and the classroom (14,15,38).

1 | HISTORIC OF EVOLUTIONARY MEDICINE

Evolutionary medicine is not a new specialty or method of practice or critique of medicine. Instead, it consists of the intersections where evolutionary insights bring something new and useful to the medical profession, and where medical research offers new insights, questions, and research opportunities for evolutionary biology (27). Evolution and medicine started an immature approximation in the late 19th century that broke up amid violent recriminations in the early 20th century (27). Thereafter, the relationship remained distant until they were reintroduced on a more mature basis (39). Evolutionary Medicine, which dates back to the early 1960s, aims to explain diseases based both on recent physiological causes (i.e. those most commonly addressed by medicine) and on more distant evolutionary causes (i.e. those responsible for the emergence and survival of useful and functional biological structures throughout the history of the planet) (37).

In the 19th century, pre-Darwinian biology was mainly descriptive. Variability was well documented, but poorly understood and, as underlined by the article "Evolutionary physiology" (40), "Physiologists are interested in how organisms work and, a subset of physiologists also wants to know why organisms are designed to work in particular ways. Unless one assumes special creation of all organisms, an understanding of such why questions requires an evolutionary perspective" (40).

EVOLUTIONARY THEORY

Evolution is perhaps the most basic scientific theory. Some would say it is the most powerful because “Nothing in medicine makes sense, except in the light of evolution” (41). Evolution acting through natural selection represents an ongoing interaction between a species’ genome and its environment over the course of multiple generations. Genetic traits may be positively or negatively selected relative to their concordance or discordance with environmental selective pressures.

Evolutionary theory insists we understand the body not as a product of design but of natural selection. Therefore, “bodies are vulnerable to disease, and remarkably resilient, precisely because they are not machines built from a plan” (14).

Yet powerful, evolutionary theory application to health and medicine is vastly underutilized. Evolution is also a “basic science” (27) and it is no exaggeration to suggest that its application in medicine could revolutionize the discipline.

1 | HISTORIC OF EVOLUTIONARY THEORY

The evolutionary theory was first applied to health by George Williams (1957), in the context of senescence. Five decades later, Randolph Nesse summarizes the evolutionary theory to medicine as “all biological traits need two kinds of explanation, both proximate and evolutionary”. The proximate explanation for a disease describes what is wrong in the body mechanism of individuals affected by it. An evolutionary explanation is completed different. Instead of explaining why people are different, it explains why we are all the same in ways that leave us vulnerable to disease” (14). Therefore, evolutionary theory generates testable hypotheses regarding how organisms should respond to environmental stimuli, and these hypotheses are widely supported in diverse species, including humans (42–44).

2 | EVOLUTIONARY THEORY IN PUBLIC HEALTH

2.1 Evolutionary theory insists we understand

As it has previously argued, our body is not as a product of design but of natural selection therefore bodies are vulnerable to disease, and remarkably resilient. They are, instead, bundles of compromises shaped by natural selection in small increments to maximize reproduction, not health” (14). Consequently, natural selection has not shaped organisms for maximum health, but rather to maximize their reproductive success (or genetic fitness). This approach helps understand why people present at clinics, but it might not help prevent illness from developing (36). Consequently, public health interventions might not always achieve exactly what they intended.

Conventionally, public health models of behavior emphasize purpose and individual autonomy. The aim of public health is to prevent disease, promote health, and prolong life in human populations through the organized efforts of society (45). It is intuitive that improving living conditions should benefit peoples' health. We can still use evolutionary principles to understand associations between behavior and health outcomes. In behavioral terms, low investment in self-preservation could be mediated by time preferences, in which short-term gains are favored over long-term rewards. Public health programs targeting infant infections or adult reproduction are thus expected to shape long-term health outcomes and disease susceptibility through influencing these trade-offs (36).

Because physicians and public health professionals deal with phenotypes, they can gain substantially from a theory that predicts phenotypic states and how they are expected to change over an individual's life course. Going beyond standard care, an understanding of each individual's ongoing life history could guide personalized decisions concerning the prevention, diagnosis, and treatment of disease (36).

3 I INTERFACE OF EVOLUTIONARY BIOLOGY AND MEDICINE

3.1 The Symbiotic Microbiota

The first insight given by the interface of evolutionary biology and medicine is that "humans coevolved with a normal community of symbiotic and parasitic microorganisms" (13).

Biologists have traditionally defined vertebrates as a group with neural crest tissue and ten organ systems. The microbiota (the naturally occurring set of microorganisms that inhabit body organs, especially the gut) is a newly recognized 11th vertebrate organ system that influences all of the other systems and communicates with them through the metabolome. Today, all vertebrates harbour large communities of microorganisms (microbiota), particularly in the gut. A noteworthy percentage of the metabolic products in human blood is microbial in origin. At least 20% of the small molecules in human blood are products of the microbiota (46).

Vertebrates arose early in the evolution of animals, about 500 million years ago, only about 20–30 million years after the Cambrian explosion (47). The trajectory of evolution that lead to human beings has a series of 19 steps in which, with each successive step, new genes arise. This provides evidence that about 65% of our genes originated with Bacteria, Archaea, and unicellular eukaryotes, including those genes that enabled animal-microbe interactions (48).

A bacterium was once a component of the ancestor of all eukaryotic cells, and much of the human genome originated in microorganisms (46). A good example is the mitochondria,

ancient bacterial symbionts with their own mitochondrial DNA (mtDNA), RNA, and protein synthesizing systems. Each human cell contains hundreds of mitochondria and thousands of mtDNAs. The mtDNA is maternally inherited and shows striking regional genetic variation. This regional variation was a major factor in permitting humans to adapt to the different global environments they encountered and mastered. Moreover, the mitochondria burn the calories in our diet with the oxygen that we breathe to make chemical energy to do work and heat to maintain our body temperature. As a by-product of energy production, the mitochondria also generate most of the endogenous reactive oxygen species (ROS) of the cell, and these damage the mitochondria, mtDNAs, and cell (49).

THE LIFE HISTORY THEORY

Natural selection shapes organisms to maximize their reproductive success (or genetic fitness). Then, life history theory was developed to predict the coordinated evolution of the traits contributing directly to fitness: age and size at maturation, number and size of offspring, number of reproductive events, and ageing and lifespan. Traits are interactions between intrinsic constraints and trade-offs. Humans and other primates have evolved particular morphological and biological traits (e.g., larger brains, slower growth, longer-lived offspring) that distinguish them from most other mammals (13). The evolution of these traits is viewed as product of interactions between intrinsic constraints and trade-offs. On the other hand, the life history theory views the evolution of the fitness traits as the product of trade-offs and extrinsic factors in the environment that affect mortality risk and resource availability. It then considers how extrinsic factors shape the combination of intrinsic traits to maximize fitness (15).

Progress at the interface of evolutionary biology and medicine has given rise to two general messages (13). The first general message is that, the view of organisms as machines whose design has been optimized by engineers is as misleading as it is deeply entrenched. Organisms are, instead, bundles of compromises shaped by natural selection to maximize reproduction, not health (15). They are thus full of unavoidable trade-offs and constraints. Trade-offs are key concepts in life history theory. Trade-offs are features inherited or acquired during development and extrinsic factors in the environment that affect mortality risk and resource availability. There are full of unavoidable tradeoffs and constraints. Major trade-offs involved were encephalization-gut size; growth-immunological defense and longevity-reproduction. Major constraints were famine and infection.

A trade-off occurs whenever a change in one trait that increases fitness is connected to a change in another trait that decreases fitness. Many trade-offs pertain to individual organisms. Overall, life is the interplay between structure and energy (49).

The availability of energy shapes the passage of each individual through life history decision nodes (e.g. how fast to grow, when to mature, and how long to live) (46).

The major functions involved in lifespan are maintenance, growth, reproduction, and defense, in which energy can be invested. Changes in allocations among these functions are shaped both by resource availability and extrinsic mortality risk, of which key components in humans include infectious disease, poverty or deprivation, and violence or conflict.

The specific decisions that constitute each individual's life-history trajectory are enacted at levels that include physiology and behavior. Furthermore, human societies generate stresses for which their biology is unprepared or mismatched (50), such as pollutants, processed foods, and sedentary environments. Many of the relevant mechanisms are already well understood to shape disease risk. These are the same mechanisms that

permit adaptation through plasticity to ecological stimuli and stresses. Both hormonal and behavioral plasticity represent mechanisms of risk management that are inherently sensitive to physical and societal stimuli (51).

Life-history theory attempts to understand ecological factors that shape strategic allocations between size versus number of offspring, reproductive effort versus body maintenance, early versus delayed reproduction, and making the best of current opportunities versus preparing for an uncertain future (52).

Strategic choices at the organismal level must emerge from information- processing within cells. Each cell must not only manage its own metabolism, second by second and minute by minute, but also coordinate its activities over much longer periods with many other cells of the same and different types. A major strategic decision involves the relative proliferation of cells contributing to muscle mass (conferring superior earning capacity but increased maintenance costs) and fat mass (a load to be carried but insurance against hard times. Additionally, choices of fuel - whether to burn or stored fat and whether to use amino acids for gluconeogenesis or to build proteins - are implicated in major life-history trade-offs, including those between investment in present reproduction and precautionary savings.

1 | THE ROLE OF HORMONES

Hormones and other circulating factors provide cues that allow cellular behavior to be matched to organismal goals. Hormones allow organisms to respond to both endogenous and exogenous environmental factors by modifying cell functions variably across tissues and organs. Hormones are now recognized to generate multiple physiological effects, a scenario known as pleiotropy (53). In each case, hormones such as insulin, leptin and cortisol implement the allocation of energy between life history functions.

Growth hormone, for example, modulates fuel choice between fats and protein (via gluconeogenesis). Increased reliance on lipids to conserve protein would be favored both during rapid linear growth and during malnutrition but the adaptive tissue-specific responses in these two situations should differ markedly as elevated growth hormone is integrated with other cues (54).

Insulin plays a key role in allocating energy across competing physiological functions. Insulin modulates the regulation of peripheral metabolism, including appetite, reproductive function, thermoregulation, and adiposity, via receptors in the brain (55). Within the brain, insulin also regulates cognitive functions such as learning and memory (56). Although muscle insulin resistance increases the risk of diabetes, it also allows the diversion of glucose from muscle to other tissues (57).

Leptin, which is secreted by adipose tissue, signals the magnitude of energy stores to the brain but also has broader functions, contributing to the regulation of reproduction,

cognitive function, and immune function (58,59). For example, leptin influences the functions of T cells, monocytes, macrophages, and natural killer cells, as well as the release and expression of cytokines and other inflammatory markers, and these molecules likewise contribute to the regulation of energy balance (59). Although early linear growth benefits long-term health and human capital (60), the association between low leptin and mortality in malnourished children indicates the short-term survival value of body fat (61).

Another influential hormone is cortisol, produced by the adrenal glands in response to diverse types of stress including illness, trauma, fear, pain, and psychosocial stress. It too affects diverse metabolic activities, for example suppressing immune function while increasing blood pressure and blood glucose (62).

Mammalian reproduction inherently brings the life-history strategies of two generations together, through placental nutrition and lactation. This interaction could be characterized as a tug-of-war over maternal metabolic resources (63), because the energy allocation decisions that are optimal for maternal fitness might not maximize offspring fitness. In such parent–offspring conflict (64), hormones now function as signals between individuals, and each party can not only read the signals of the other, but can also potentially manipulate them with their own hormonal secretions. Placental lactogen promotes maternal insulin resistance, allowing the fetus to gain from prolonged increases in maternal blood sugar levels after meals (54). This thrifty phenotype represents a short-term adaptive response to poor energy availability (65). Although such plasticity might be adaptive, especially in the context of reproduction (66) it can also impose metabolic costs, accelerating the rate of ageing.

2 | TRADE-OFF LONGEVITY-REPRODUCTION

Bodies exist to achieve maximal reproductive and genetic fitness, not to be maximally healthy or live long (14). This natural selection imperative means that caloric expenditure and time must be conserved, which can conflict with health goals. In fact, reproductive success can diminish health outcomes. In high income countries low socioeconomic position correlates with earlier reproduction, and poorer health status could be an important explanatory variable. There are studies showing that parental survivorship declined in proportion to the number of children produced, more strongly in mothers than fathers (67). However, the magnitude of this effect varies by living standards (68), and reproduction might protect against some cancers (66).

A link between deprivation and early age at first birth also remains across populations worldwide (69). Data from England (2009 to 2011) showed that, living in areas with the highest deprivation was associated with a life expectancy 7 years shorter for women and 9 years shorter for men, compared with those in the least-deprived areas (70). Hence,

early reproduction in women of low socioeconomic position might reflect both their lower expectancy of a healthy life and the absence of benefits of waiting to reproduce, since they typically have fewer chances to capitalize on educational and career opportunities. In behavioral terms, low investment in self-preservation could be mediated by time preferences, in which short-term gains are favored over long-term rewards.

3 I TRADE-OFF REPRODUCTION AND SURVIVAL

The reduced stress improved women's fertility, and higher birth rate, which led malnutrition among their offspring. This was proven by an initiative of providing local wells, in rural Ethiopia. By working to reduce the energy burden on women carrying large loads of water (for 19km), it was expected to improve women's nutritional status and hence their children's. Instead, In turn, it increased energy investment in reproduction without nutritional improvements. This indicates decreased investment in homoeostasis, and this might contribute to elevated NCD risk in populations of low socioeconomic position (71).

The trade-off between reproduction and survival (maintenance or defense) shapes the rate of ageing and NCD risk(51). Such trade-offs also apply across generations. Throughout (72) sub-Saharan African countries, the odds of child survival fell in relation to the number of offspring produced by the mother (73). Similarly, there are studies showing that parental survivorship declined in proportion to the number of children produced, more strongly in mothers than fathers (67). The magnitude of this effect varies by living standards (68), and reproduction might protect against some cancers (66).

4 I TRADE-OFF IMMUNE FUNCTION VERSUS GROWTH

The major functions involved in lifespan are maintenance, growth, reproduction, and defense, in which energy can be invested. Changes in allocations among these functions are shaped both by resource availability and extrinsic mortality risk, of which key components in humans include infectious disease, poverty or deprivation, and violence or conflict. For example, the trade-off between reproduction and survival (maintenance or defense) shapes the rate of ageing and NCD risk (51). Once the energy is available, human metabolism is a tug-of-war between managing beneficial microbes, excluding detrimental ones, and channeling as much energy as is available into other essential functions (e.g. growth, maintenance, reproduction). This tug-of-war shapes the passage of each individual through life history decision nodes (e.g. how fast to grow, when to mature, and how long to live) (46).

The immune function versus growth is a trade-off especially relevant to public health. Developmental exposure to infectious diseases shapes the entire life history strategy, and might propagate effects to subsequent generations (74). Developmental exposure to infectious diseases shapes the entire life history strategy, and might propagate effects to

subsequent generations (74). Immune function is metabolically costly (75); for example, in children, each degree of temperature rise from fever increases metabolic rate by 11·3% (76), hence the costs of fighting infections impair child growth (77). Then, nutritional interventions to resolve stunting might be ineffective unless also reducing the burden of infections and parasites (78). This relationship can account for epidemiological associations linking secular declines in infant mortality rate (a proxy for the energy costs of immune function in the survivors) with secular increases in adult height and longevity (79).

5 | PLASTICITY

Life history theory models phenotypic evolution in general. Conventionally, evolutionary perspectives of human phenotypic variability emphasize our genetic variability and diverse components of plasticity. Plastic responses to environmental stimuli include physiological adaptations implemented by homoeostatic feedback loops that can react in seconds or minutes, acclimations (eg, adjustments to altitude) that can react in days to weeks through changes in the setpoints of feedback loops, and finally, developmental plasticity, in which reactions usually last a lifetime (16,36). We can use evolutionary principles to understand associations between behavior and health outcomes. Therefore, the medical importance of plasticity is most apparent in the developmental origins of adult health and disease(80,81).

Organisms are bundles of compromises shaped by natural selection and, humans and other primates have evolved particular morphological and biological traits. The evolution of these traits is viewed as product of interactions between intrinsic constraints and trade-offs features inherited or acquired during development, and the environment (extrinsic factors) that affect mortality risk and resource availability (18).

The evolution of H. erectus in Africa is widely viewed as a “major adaptive shift” in human evolution (82). In fact, humans appear to be distinctive in their developmental changes in body composition and, since Hominins that lived in East Africa, we experienced a (a) marked increases in both brain and body size, (b) the evolution of human-like body proportions, and (c) major reductions of posterior tooth size and craniofacial robusticity (83,84).

6 | EXPENSIVE-TISSUE HYPOTHESIS AND THE BRAIN-GUT TRADE-OFF

The most important of the developmental changes in body composition is our high levels of encephalization (large brain:body mass). Over the course of the last three million years, hominin brain sizes tripled. It is often taken for granted that the benefit of a larger brain is an increase in “intelligence” that makes us stand out among other mammals, including our nearest relatives, the primates. It appears that major expansion of brain size in the human

lineage is the product of synergistically interacting dietary/nutritional and social forces (18).

The lack of correlation between Rest Metabolic Rate and relative brain size in encephalized mammals raises the question of how the increased energetic demands of larger brains are compensated. The “expensive tissue hypothesis” posits that the metabolic accommodation of large brains is achieved by a reduction in the mass/sizes of other tissues with high-energy demands. The brain-gut trade-off hypothesis suggests that the massive expansion of the brain in humans came at the expense of the gastrointestinal tract (85). Besides the reduced gut sizes, and high activity budgets, the evolution of our large brain sizes was consequent to major energetic and dietary shifts (18).

6.1 The Role of Nutrition in Brain Expansion

Dietary/nutritional forces synergistically interacting with social forces appears to be the major factors for expansion of brain size in the human lineage (18). The first task for greater brain would be the energy yelding and the second task would be the raw material for the extra-tissue structure. The central nervous system accounts for only 2% of the whole body mass but 60% of it dry mass is fat, 25% long-chain fatty acids and 24% cholesterol (86). In the case of humans, brain expansion was associated with changes in diet, foraging, and energy metabolism. The first marked expansion occurred with the appearance of the genus Homo. Improved diet quality, allomaternal subsidies, cognitive buffering (by earlier weaning and longer juvenile periods), reduced costs for locomotion and by cooperative behavior, and reduced allocation to production, all operated simultaneously, thus enabling the extraordinary brain enlargement in our lineage. Although dietary change was not being the sole force responsible for the evolution of large brain size, the exploitation of high-quality foods likely fueled the energetic costs of larger brains and necessitated more complex behaviors that would have selected for greater brain size (18).

ENVIRONMENTAL CONSTRAINS FOR EVOLUTIONARY TRAITS

The main dangers threatening our ancestral survival were famine, infection, and physical trauma. Therefore, survival of multicellular organisms depends on the organism's ability to these stress adaptations, a high energy demand processes. To cope with the injury responses, a coordination of neuroendocrine, energy storage, water economy and immune systems are adapted (22).

1 | FAMINE

In ancient time, food supply was never consistent then, it is contended that the human ancestors had cycles of feast and famine, punctuated with obligate periods of famine, and certain genes evolved to regulate efficient intake and utilization of fuel stores (19). During famines, individuals with the thrifty genotype would have a survival advantage because they relied on larger, previously stored energy to maintain homeostasis (87,88). The physiological adaptation that is induced by the fasting state includes increased lipolysis, lipid oxidation, ketone body synthesis, endogenous glucose production and uptake and decreased glucose oxidation. These processes are crucial for survival and serve to protect the organism from excessive loss of protein mass (89).

2 | INFECTION

To cope with the injury responses, a coordination of neuroendocrine, energy storage, water economy and immune systems are adapted. The formation of a systemic and/or local tissue-specific insulin resistance due to inflammatory cell activation may actually be a protective mechanisms that co-evolved with the repartition of energy sources within the body during times of stress and infection. The time frame of an organism's response to the acute inflammatory episode may reflect an adaptive natural selection mechanism for the coordination of the immune and energy system to fight against infection (22).

THE THRIFTINESS CONCEPT

In general language thrifty genes implies some degree of prosperity deriving from earlier frugality and careful management of resources (87). Humans represent a thrifty species relative to some other mammals. This indicates that metabolic adaptations had a crucial role in the emergence of present day Homo Sapien lineage, in particular in buffering reproduction from ecological stochasticity (87). The imprinted thrifty-genes influence not only the balance of tissues within bodies but also basic metabolic parameters. Its use in reference to human metabolism spread after an influential article by James Neel proposed that certain genes relevant to metabolism could have been favored by natural selection in certain environmental conditions (26) such as famine, infection, wound healing and body dehydration.

1 | ENERGY THRIFTINESS

Our brain volume tripled over the course of two million year period and, our high levels of encephalization (large brain:body mass) is often taken for granted that the benefit of a larger brain is an increase in “intelligence” that make us stand out amongst other mammals, including our nearest relatives, the primates (90). Brain makes only 2% of the body, but expends 20% of the total rest-energy expenditure! For doing it so, human infants are born altricially (relatively underdeveloped for their age), and unlike other primates, continue rapid brain growth into early postnatal life (91).To provide energy reserves for these high metabolic demand, dedicated fat-storing cells were necessary, because the tissues of the lean body mass lack the storage capacity to meet the fuel demands imposed by famine. Hence the evolution of adipocytes served the purpose of extending survival during the recurrent cycles of famine (92). To support the large, rapidly growing brains, human infants are born with high body fat levels, and continue to gain fat during the first year of postnatal life (18). Normally, a variable amounts of extra fat are safely stored subcutaneously, either locally hip and thigh (in adults) or spread over total body subcutaneous (in children), where it confers a metabolically protective reserve in both genders and supports pregnancy and lactation in females (93).

The ability to effectively detect, metabolize, and store fats likely provided tremendous selective advantages to our hominid ancestors, allowing them to expand into diverse ecosystems around the world (94). For so, it has been hypothesized that genes responsible for energy regulation and preservation have been positively selected. These thriftiness has been described not only in storing and sparing muscle glycogen by prioritizing fatty-acid oxidation as energy-yielding substrate (18) as well as by providing free-cholesterol and conjugated lipids, as building blocks for structuring the brain (86). The human encephalization has allowed also an extended lifespan and therefore, for the longevity, the regulation of

energy storage is critical for organism's fight against famine, infection and physical stress (18).

2 | THRIFTINESS OF FATNESS

The central nervous system accounts for only 2% of the whole body mass but expends 23% of our daily energy (18). To accommodate the extraordinary energy demands of the developing infant brain, human infants are born with an ample supply of body fat (95). Fatty acids provide doubled kcal/g than CHO or protein and are stored anhydrously either occupying intracellular or inter organs spaces, insulating parenchymal organs and working as subcutaneous cushion. We have higher levels of body fatness than other primate species and, at ~15%–16% body fat, human infants have the highest body fat levels of any mammalian species (96).

In hominoids, features such as nutrient requirements and digestive physiology appear to be genetically conservative" (Milton 2000). With the evolution of Homo erectus, our ancestors began a new lifestyle oriented around a combination of meat eating and gathering (82,97). Key genetic mutations during later hominid evolution were critical to promoting the enhanced lipid metabolism necessary for subsisting on diets with greater levels of animal material.

The evolutionary conservation of ancestrally selected physiological traits is likely, because "Humans are not self made creations dietary, but rather have an evolutionary history as anthropoid primates stretching back more than 25 million years, a history that shaped their nutrient requirements and digestive physiology well before they were humans or even proto-humans. Hence, compared to large-bodied apes, humans have an enhanced capacity to digest and metabolize higher fat diets. Our gastrointestinal tract, with its expanded small intestine and reduced colon, is quite different from those of chimpanzees and gorillas and is consistent with the consumption of a high-quality diet with large amounts of animal food. It has been shown that the evolution of key "meat-adaptive" genes in hominid evolution were critical to promoting enhanced lipid metabolism necessary for subsisting on diets with greater levels of animal materia (98).

Along with the critical selection for key "meat-adaptive" genes allowing our hominid ancestors to more effectively exploit diets with higher levels of animal fat (99), there are evidences highlighting the remarkable capacity of the human brain and sensory system for accurately assessing the energy content of potential food items. Thus, associated with the evolution of our high-quality diet, the need for an energy-rich diet also appears to have shaped our ability to detect and metabolize high-fat foods. Therefore, we show strong preferences for lipid-rich foods. It has been shown that these preferences are based on the smell, texture, and taste of fatty foods (100–102). In sum, the ability to effectively detect,

metabolize, and store fats likely provided tremendous selective advantages to our hominid ancestors, allowing them to expand into diverse ecosystems around the world (94).

Following high-fat intake, it is induced a diet-induced thermogenesis, including the increased expression of uncoupling proteins (UCPs) which acts as a defense mechanism against weight gain. The increased heat produced by UCPs not only helps increase energy expenditure but also promotes satiety, thereby establishing energy balance. Diet regimens with pure fat, the so-called ketogenic diets, have been introduced and demonstrated to cause rapid weight loss. One reason for this is the difficulty these patients demonstrate to overeat pure fat without any carbohydrates. Therefore, sucrose in a mixture with fat is reported to weaken the satiety signals for fat. Then, the long-term effects of high-fat diets are similar to the low-fat diets in regard to weight loss and metabolic parameters (103).

3 | THE THRIFTINESS OF CHOLESTEROL

Cholesterol and related sterols (ergosterol in yeast, phytosterols in plants) is considered a hallmark of eukaryotes, and may even have triggered the evolution of multicellular organisms. Cell needs cholesterol into the composition of its membrane as a precursor for steroid hormones, vitamin D, and bile acids. Therefore, yet often considered in a negative light, cholesterol is an essential molecule with unusually diverse functions. The exclusivity of cholesterol to the membranes of animal cells suggests that cholesterol and a diversity of lipid species have evolved to confer the necessary intrinsic properties of biological membranes, such as flexibility and selective permeability. Overall, cholesterol is an essential membrane reinforce (104).

During evolution, the plasma membrane came to play an additional, highly specialized role in the central nervous system (CNS) as the major architectural component of compact myelin. As a consequence, in the human the mean concentration of unesterified cholesterol in the CNS is higher than in any other tissue (~23 mg/g). The central nervous system accounts for only 2% of the whole body mass but contains almost a quarter of the unesterified cholesterol present in the whole individual (105). The evolutionary adaptation of the cholesterol-rich plasma membrane to form compact myelin made it possible to “wire” the complex brain with numerous relatively small-diameter, low-capacitance axons that manifested very high conduction velocities (105).

Although the evolution of myelin largely solved the problem of action potential conduction velocity, this insulatory layer on axons did add additional volume to the CNS, particularly in the large brains of primates, where there was massive expansion of the neocortex (18). Over a very large range of brain sizes, the volume of the neocortex increased from only 16% of the volume of the whole brain in small animals to 74% in Hominoidea. In contrast, the relative volume of the cerebellum remained constant at 13% of whole brain

volume, regardless of the absolute size of the brain (106,107). As the size of the neocortex progressively evolved, so also did the volume occupied by myelinated nerve fibers, white matter and the size pool in the CNS (86). Therefore, although solving the problem of nerve conduction velocity, the disproportionate increase in brain size during fetal and neonatal development created a challenge that ultimately dictated when brain growth and myelination could take place. That is because the cross-sectional area of the female pelvis limited the degree of development of the CNS before birth by limiting the size of the head that could pass through the birth canal (105).

Head size is related to the degree of myelinization in the brain where the mean concentration of cholesterol makes the difference. For the animals that are not noted for their intellectual capacity, the early myelination allows the newborn to be immediately mobile so that it can be led away from the birthing site before attracting the attention of local predators (e.g. guinea pig and sheep). Species, represented by the mouse and hamster have essentially no myelination in the brain and therefore are nearly helpless at birth. The human, also born essentially helpless, follows a similar pattern of myelination, although a number of years, rather than weeks, are required for the average concentration of cholesterol in the brain to increase. However, in the 3 weeks after birth, cholesterol rapidly accumulates in the CNS (108).

Adding to the roll of the well diffused role of cholesterol, there is also evidence that sterols like cholesterol may have in fact been a protective response to the increasing levels of molecular oxygen in earth's atmosphere (109). An intricate link between sterols and oxygen is the idea that sterols are oxygen sensors in mammalian cells (110). The surveillance role of sterols in sensing oxygen, becomes cholesterol an active defense against this potential hazard. Cholesterol has even been considered to act as an antioxidant (111). Synthesis of cholesterol is an extremely oxygen-intensive process and requires sufficient terrestrial oxygen to proceed. To make one molecule of cholesterol, 11 molecules of oxygen are needed (112). Because oxygen is a necessary component in cholesterol production, the idea that cholesterol in turn may limit oxygen uptake by eukaryotic cells has a certain elegant symmetry to it. Indeed, there are several studies suggesting that cholesterol limits oxygen diffusion across membranes (113–115).

The cholesterol's general barrier function in cell membrane is to exclude polar molecules and, although oxygen is not polar, its diffusion across mammalian cell membranes is considerably influenced by the cholesterol content of the plasma membrane (113).

4 | THE THRIFTINESS OF INSULIN RESISTANCE

In processes associated with insulin resistance such as famine, infection, trauma and physical stress, plasma levels of glucose are elevated to provide energy sources to

maintain the function of vital organs (heart, brain and immune cells). Therefore, negative regulation of insulin signaling could be viewed as a physiologic 'adaptive mechanism" that is activated in certain unfavorable conditions and pregnancy (116,117).

In the sense of human evolutionary history, insulin resistance may be an essential part of normal homeostasis to facilitate redirection of nutrients to pivotal organs as a physiological adaptive mechanism to promote our ancestor's survival (118,119). Humans are extremely sensitive to glucose deficits, due to the large energy requirement (glucose) of the brain (116) and the glucose-dependent blood-cells, gonads, retina, mucosal and fibroblasts.

Glucose uptake by muscle, adipose and liver cells, can be obtained through activation in these cells, of a cascade of molecular signals, promoting the gene expression of GLUT4 (120). On rest state conditions, the major tissues of muscle, adipose and liver are GLUT-4 dependent for blood-glucose clearance, which is an insulin-dependent process. Skeletal muscle takes 80% of insulin-dependent glucose uptake. Consequently, insulin resistance promotes reallocation of glucose from major tissues (skeletal muscle, adipose tissue and liver) to the brain, tissue repair and immune system (20). As a result of insulin resistance, plasma levels of glucose are elevated to provide energy sources, maintain the function of vital organs, and combat infection (65,89,121).

The main factors responsible for the loss of insulin sensitivity in skeletal muscle are starvation, hypocaloric nutrition and immobilization. In healthy subjects, insulin resistance and marked alterations in substrate utilization induced by a few days of starvation or hypocaloric nutrition are more pronounced with combined immobilization (122–124).

In the early development of both, the endocrine and exocrine pancreas, and in later differentiation and function of the β-cell, there is a critical role played by Pdx-1, a homeo domain-containing transcription factor. Progressive decrease in Pdx-1 expression manifests as defective glucose homeostasis and increased oxidative stress in aging IUGR (125). Perinatal nutrient restriction resulting in IUGR leads to silencing histone modifications in skeletal muscle which in turn directly decrease GLUT4 gene expression, effectively creating a metabolic knockdown of this important regulator of peripheral glucose transport and insulin resistance and contributing to the adult T2D phenotype (57).

Concerning the muscle tissue, the promoter region of GLUT is the myocyte enhancer factor 2 (MEF2), whereas MyoD is responsible for GLUT 4 expression during myoblast to myocyte differentiation. These two proteins synergistically enhance skeletal muscle GLUT4 transcriptions and gene expression (126). It is accepted that an ancestral polymorphism of the muscle glucose transporter (GLUT4) spread in the past to save this sugar from muscle in favor of the brain in periods of famine. In fact, IUGR is associated with an increase in MEF2D (form that acts as an inhibitor) and a decrease in both MEF2A (that acts as an activator) and MyoD (a co-activator) binding to the GLUT 4 promoter in skeletal muscle (57).

5 | THE THRIFTINESS OF BODY FLUIDS PRESERVATION

With the hot and humid climate, like in eastern Africa, effective heat dissipation is essential in hot environments and is achieved most efficiently through evaporative heat loss (127). However, sweating due to the hot climate and excessive labor activities can lead to a large loss in the amount of salt and water, and eventually lead to hypovolemia, a threat to human survival. In addition, human and nonhuman primates living in ancient times had very low salt intake available. Low salt intake and large salt losses due to sweating had created robust salt appetite and renal sodium conservation, which were essential to survival (21). Then as results of natural selection, the survival pressures drove our evolution to shape a genotype, which favored/promoted energy-saving and sodium/water preservation. Since regulation of energy storage and the preservation of body fluids are critical for organism's fight against famine, infection and physical stress, it has been hypothesized that genes responsible for energy regulation and sodium preservation have been positively selected (128). It is well known that sodium is the main determinant of body fluid distribution, once sodium accumulation causes water retention. Hence, sodium transport through various nephron segments, is quite important in regulating sodium reabsorption and blood pressure (129).

Like energy storage, insulin-mediated sodium preservation may be an adaptive mechanism for human survival during ancient time. In fact, in addition to its metabolic effects, insulin induces vaso-relaxation by stimulating the production of nitric oxide (NO) in endothelium and regulates sodium homeostasis by enhancing sodium reabsorption in the kidney. ENaC and sodium proton exchanger type 3 (NHE3) are main mediators to regulate sodium reabsorption in renal tubules. It has been shown that insulin can regulate ENaC and NHE3, therefore increasing renal tubular sodium reabsorption (129,130). The increased blood pressure by insulin resistance may contribute to increased blood perfusion to the brain during starvation and infection, and to the fetus during pregnancy (117,121).

6 | THE THRIFTINESS OF INFLAMMATION

Infection, mechanical force, chemicals, and extreme heat or cold can damage tissues, causing the nonspecific process of inflammation. Progressive destruction of the tissue would compromise the survival of the organism, therefore inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the (immunological or) healing process. For though, acute inflammation can be understood as a thriftiness of survival (22).

It is known that an activation of the innate and adaptive immune system demands, not only high energy consumption and, the acute inflammatory episode may cause water loss. To cope with the injury responses, a coordination of neuroendocrine, energy storage,

water economy and immune systems are adapted. Thus in addition to its immunological thriftiness, acute inflammation has also metabolic thriftiness, by its negative regulation of insulin signaling through inflammatory cytokines released from activated immune cells (22). The formation of a systemic and/or local tissue-specific insulin resistance due to inflammatory cell activation may actually be a protective mechanisms that co-evolved with the repartition of energy sources within the body during times of stress and infection and, as results of natural selection, the survival pressures drove our evolution to shape a thrifty genotype, which favored/promoted energy-saving and sodium/water preservation (121).

7 | THE THRIFTINESS OF PHYSICAL ACTIVITY

Paralleling the tremendous brain growth we assumed an upright position (131). Aerobic physical activity became an increasingly important element of the human lifestyle beginning approximately 1.8 million years ago. This lifestyle contrasts with the more sedentary ape-like lifestyles of the earlier hominin genus, Australopithecus, who are reconstructed to have ranged much shorter distances than H. erectus (97,132). In fact, hunter-gatherers cover greater distances in single-day foraging bouts than other living primates, and these treks require high levels of cardiovascular endurance (133,134). Foraging means relying on food provided by nature through the gathering of plants and small animals, birds, and insects; scavenging animals killed by other predators; and hunting. In addition to long foraging distances, endurance running (ER) is thought to be an important component of this early hunting and gathering lifestyle (133,135,136).

There is evidence that a change in body shape during the evolution of the genus Homo is consistent with skeletal adaptations for ER, and differs from the more ape-like body shape of earlier hominins (133,137). Traits that improve ER performance, but seem to have little effect on walking performance, include increased semicircular canal radii, increased joint surface areas in the lower, but not upper, limbs, and the possible convergent evolution of many skeletal and neurobiological traits that improve endurance performance in mammals and humans (133,135,136,138–140). Thus, beginning with the evolution of H. erectus, our ancestors became endurance athletes, regularly engaging in high levels of aerobic physical activity (132).

Independently of fed state, prolonged endurance exercise elicits a variety of metabolic and morphological gene expression including those related to mitochondrial biogenesis, fast slow fiber-type transformation and substrate metabolism. In contrast, heavy resistance exercise stimulates synthesis of contractile proteins responsible for muscle hypertrophy and maximal contractile force output (141).

As practical results, the famine-induced insulin resistance may be reversed by exercise in order to conserve muscle glycogen stores by oxidizing greater quantities of

fatty acids. This 'thrifty' regulation allows skeletal muscle to consume enough energy and permitted our ancestors to continue intense physical activities to hunt for food, despite prolonged fasted states (142).

The fact that both feast–famine and exercise–rest cycles produce oscillations in glycogen concentration implies that some of the glycogen cycling regulatory mechanisms for the above two hunter-gatherer situations could be common (143). In fact, the human body only stores about 1500 kcal of glycogen but it can store 120,000 kcal of triglyceride, posing the question as to whether the enzymes involved in such a small storage of glycogen could play a role as "thrifty" genes since 1500 kcal can hardly supply even one day of total caloric output (30). Oscillations of muscle glycogen and triglyceride levels with physical activity–rest cycles during feast–famine over tens of thousands of years selected some genotypes and genes to oscillate, some of which might also play a role in efficiency during fuel usage (142). Studies in experimental models manipulating muscle glycogen content with exercise have revealed several possible candidates as "thrifty" genes. Among the genes that efficiently conserve the utilization of muscle glycogen were pyruvate dehydrogenase kinase-4, hexokinase, IL-6 and HSP72 (144–146). It is probable that evolution selected these genes for glucose storage and conservation in order to rapidly provide the energy necessary for immediate tasks related to muscle work and survival (30).

Skeletal muscle takes 80% of insulin-dependent glucose uptake. Hence muscle insulin resistance conserves glucose for utilization by the central nervous system decreasing the amount of muscle protein needed to be converted to glucose (neoglucogenesis). The metabolic process of insulin resistance may be reversed by exercise in order to conserve muscle glycogen stores by oxidizing greater quantities of fatty acids. This 'thrifty' regulation allows skeletal muscle to consume enough energy and permitted our ancestors to continue intense physical activities to hunt for food, despite prolonged fasted states (30). The increased glucose uptake by muscle during and immediately after exercise, can be obtained insulin-independently through activation in muscle cells of a cascade of molecular signals, promoting the gene expression of GLUT4 (120).

Cahill & Owen (1968) (147) theory postulates that the more insulin resistance an individual, the more efficient will be his ability to decrease proteolysis (and preserve lean body mass) when faced with caloric deprivation. The more efficient one in conserving muscle protein the better changes to withstand prolonged periods of deprivation, to be able to hunt successfully and to escape if preyed upon. Summing up the mentioned theories, relative insulin resistance evolved to aid metabolic partitioning between physical activity and other functions during constrained energy supply (148).

Physical exercise promotes also several beneficial cardiovascular effects mainly by reducing or preventing oxidative stress and inflammation (30). By decreasing intracellular FFA and metabolites the reactive oxygen species (ROS) generation is decreased. The

vasodilatation and anti-oxidant effects are mainly by increasing nitric oxide (NO) bioavailability (149,150). Aditionally, there are several features of acute exercise and chronic exercise training that suggest that exercise may reduce the availability of endogenous TLR4 ligands, decrease the expression of TLR4, and decrease the activation of TLR4 signaling (151,152). Moreover, during exercise, contracting skeletal muscles release anti-inflammatory myokines (IL-6, IL-10 and IL-1ra). IL-6 inhbits TNF-α production in adipose tissue and macrophages (153). The overall anti-inflammatory effects of physical activity and exercise training from a metabolic and systemic signaling perspective, includes skeletal muscle to utilization of fatty acids, TLR4 signaling, and myokine/adipokine effects (22).

ENVIRONMENTAL CONSTRAINTS AND LIFESTYLE TRANSITION

Before Homo sapiens evolved, our hominine ancestors foraged for millions of years. Humans and other primates have evolved particular morphological and biological traits (e.g., larger brain, slower growth, longer-lived offspring) that distinguish them from most other mammals. Regarding Darwin's theory of evolution, it can be assumed that the process of natural selection favored those individuals who had the capacities conducive for the gathering of the available food supply. The mobility, the freeing of the hands as he evolved to an erect stature and the stereoscopic vision most certainly contributed greatly to this task of survival (154).

Advances in genetics and archaeology over recent decades have transformed our understanding of the ancestry and migration history of the primitive humans. Coalescence is a process of actual DNA being replicated back towards past. According this theory, all our current-genome variations (polymorphisms) are derived(alleles frequency) from our ancestral. By summing up coalescence to statistic data one can set up a "haplotypes tree" where each haplotype is an unit that assembles a set of inherited genes and the "tree", points towards the evolutionary-pathway of the DNA segment. Today there are "haplotype-trees" available for nuclear DNA, showing the genome homology of humans. There is now general agreement among paleoanthropologists, comparative morphologists, and molecular systematists that humans are most closely related to chimpanzes (98.8%), followed by gorillas (98.6%), and then orangutans (97.6%) (155).

Complementary, the mitochondrial haplotypes (mother inheritance) obtained from inhabitants living in the 4 continents, allowed us to know that Homo sapiens began their geographic diaspora 200,000yrs ago, from the deserts of Tanzania (northeastern Africa), reaching the Brazilian region much later on (10,000-20,000yrs ago) (155). Then, since about 100,000 years ago humans have started to spread across the whole world to become the only Homo species currently inhabiting this planet. The dispersal of modern humans out of Africa is now widely accepted however, the route taken across Eurasia are still disputed. The coalescent-based analysis revealed strong evidence for distinct demographic expansions in Europe, southeastern Asia, and sub-Saharan Africa within the past 10,000y (24).

The "Out-of-Africa" diaspora necessitated adaptation to new conditions of existence. Changes in physical characteristics gave rise to the concept of "race," which is however better described by "geographical location" of origination as shown by studies of human genetic variation (23).

The evolution of many distinctive human characteristics, such as our large brain sizes, reduced gut sizes, and high activity budgets, suggest major energetic and dietary shifts. The experienced tremendous brain growth and assumed upright position, have coincided with a change from a vegetarian to a hunting-gathering omnivore–carnivore (18). Because of their high costs, large brains are rare and are achieved only when animals

are under strong selection. In the case of humans, there have been two environmental pressure associated with the two major periods of human brain expansion. The first occurred with bipedal running and, the second period is coincident with the domain of fire and the introduction of cooking (18).

In the 5-7 million-year period since the evolutionary emergence of hominins (bipedal primates within the taxonomic tribe hominine) > 20 species may have existed. During the Paleolithic era and the emergence of today's sole Homo species, our ancestors, including Homo sapiens(200.000 years ago), survived as hunter-gathers for approximately 84,000 generations, Thereafter, the agricultural domestication era lasted about 350 generations and, 7 generations further (200 years ago) the industrial era and agrobusiness have distanced even more the nutrition from its primate and Paleolithic ancestors (20). The different food systems and diets are part of the diverse ways of life affect people's levels of physical activity, their body composition and stature, their life expectancy and patterns of disease. In the nutritional field, nutrients and bioactive food components can modify epigenetic phenomena and alter the expression of genes at the transcriptional level. Humanity's gene pool was selected when man's remote ancestors lived as stone age hunter-gatherers. In junction with this discordance between our ancient genetically determined biology and the nutritional, cultural, and activity patterns in contemporary western populations, many of the so-called disease of civilization have emerged and among them the modern nutrition related diseases (156).

The environment in East Africa at the Plio-Pleistocene boundary was becoming much drier, resulting in declines in forested areas and an expansion of open woodlands and grasslands (157–159). Such changes in the African landscape likely made animal foods an increasingly attractive resource for our hominid ancestors (160). These changes in the relative abundance of different food resources offered an opportunity for hominids with sufficient capability to exploit the animal resources. Compared with hunting in the savanna, food from the land–water ecosystems is relatively easy to obtain and rich in iodine, vitamins A and D, and ω3 fatty acids from both vegetables and fish. Each of these nutrients has important functions in brain development and growth. Exploitation of this ecosystem, and its abundant "brain food," might be at the basis of our remarkable brain growth during the past 6 million years of evolution since our common ancestry with the present chimpanzee (18,161,162). There is good evidence to show that the evolution to H. sapiens took place on an ω3-rich diet from East-African ecosystems that were notably located in places where the land meets freshwater (99,163). It has become clear that the intake of the parent EFA and their chain elongation/desaturation metabolites, the so-called LCPUFA (≥20 straight-chain carbon atoms and ≥3 methylene-interrupted cis-double bonds) is important to our health across the entire life cycle (30).

During the Paleolithic era and the emergence of today's sole Homo species, our

ancestors, including Homo sapiens (200.000 years ago), survived as hunter-gathers for approximately 84,000 generations, eating wild animal-source foods (lean meats, internal organs, bone marrow, but no dairy) and uncultivated plant-source foods (mostly fruits, non grain, vegetables, nuts, but no legumes) (164). The gather-hunter exhibited a diet usually high in animal sources from insect to large animal, high in protein not fat because the animal were lean, moderate amounts of starchy foods, high in dietary fiber and low in sugar, mostly from fruits and honey. The diets were diverse and high in micronutrients. People in gather-hunter societies were necessarily physically active, often tall and usually lean (excepted chiefs and olds or incapacitated that were overweight or obeses) (20). Life expectancy in those people was usually low. Paleolithic people usually did not survive into what we call later middle age so our ancestors did not live long enough to develop cancer, heart disease and other chronic illness (165).

The Out-of-Africa Diaspora has largely taken place via the coastal lines (166) after the crossing of the Gilbraltar Strait to Eurasia and, through Siberia, the Bering Strait to America (167).

Beginning as early as 12 thousand years ago (kya), multiple hunter-gatherer populations began developing agriculture and animal domestication. Food production quickly spread to neighboring regions (168). What began as a rebel way of life in the Middle East was ultimately adopted around the globe and eventually drove the hunter-gather lifestyle into extinction (164). Cultivation of wheat first developed around 9000 years ago in the fertile crescent of the Middle East including Mesopotamia/Iraque. These systems also developed independently in Asia with rice as the staple food and in Americas with corn (maize) as the staple (20).

The key factor in the Peasant-agriculture systems is land settlement, itself determined by the cultivation and building of crops and also animals, birds and fish for consumption and use. Surplus food was stored for consumption in winter and during hard times. Food preparation included fermentation used for foods as well as for the production of alcoholic drinks. Peasant-agricultural societies diets also may be diverse and high in micronutrients (20).

Agriculture enables the development of towns and then cities. The people subsisted on the food they produced and the surplus fed the community living within the walls, refuge for the farmers during wars, this crowding caused a sharp rise in infectious diseases. However even then their average life expectance was probably little longer than the hunters-gatherers. The peasant-agriculturalists were physically active by building fields systems sowing, harvesting and stoning crops. Though they were usually short and lean largely because of the nature of their dietary staples. However the prosperous specially those whose land where farmed by others may quite often become overweight or obese. In general, it is accepted that agriculture diminished dietary diversity and, at the same time fuelled population growth

(169). The rise of agriculture during the Neolithic period has paradoxically been associated with worldwide population growth despite increases in disease and mortality! To reconcile this Neolithic demographic transition paradox, it was proposed that the spread of agriculture involved a life history quality–quantity trade-off whereby mothers traded offspring survival for increased fertility, achieving greater reproductive success despite deteriorating health. Thus, mothers who transition to agriculture have higher reproductive fitness (170).

Seven generations further (200 years ago), the industrial era and agrobusiness have distanced even more the nutrition from its primate and Paleolithic ancestors. Urban-industrial system began in Europe in the 18th century with distinct characteristics from the former two others. The original purpose was to ensure reliable and adequate supplies of food of an agreed minimum nutritional quality to entire populations. Technology has been the main driving force behind these systems. The technology included food-preservation, bottling, canning, refrigeration and packing, extensive use of sugar and salt, and eliminate perishable qualities in fresh foods. Steel roller mills (invented in 1870s) separate the components of wheat and enable production of uniform quality white bread which has became a staple. Sugar derived from cane was the most profitable edible cash crop. Food hydrogenation which converts oils to hard fats has made margarine a basic item of food and provides ingredients used in the manufacturing of many processed foods. Refrigeration and other technologies has made meat, milk and their products cheap and plentiful all year round. The development of railways and, an efficient urban-industrial food systems can ensure the constant supply of food to all sections of the population even to the lowest income and marginalized groups. In higher income countries and regions this together with basic public health initiatives has helped to greatly reduce rates of nutritional deficiencies (20).

Overall, urban-industrial food system generate relatively energy dense diets, these are fairly high in meat, and milk and their products, and in total fats, hardened fats, processed starches and sugars, salt, baked goods, soft drinks and often also alcoholic drinks. As a result people become generally taller and heavier. Moreover this food system improved people's strength and health in early life, doubling the average life expectancy since 1800 and increased global population 6.5 times since 1800 to 2006 (20). However, in the second half of the 20th century attention focused on the apparent ill-effects of these food systems on people mostly in later life. Thus in the last decades of the last century the demographic, nutritional and epidemiological transitions that had until then largely been apparent only in higher income countries became global (20).

Roller-milling has reduced the fiber content of cereal grain- based foods so that total fiber intake has decreased to levels much below those of agriculturalists, and hunter-gatherer primates. The low intake of fiber and its sources whole grain, fruits, and vegetables continued with the digital age (2 generations ago). The modern diet, which is inadequate in whole grain, when compared with the metabolic potential of our digestive system, is

probably one of the causes of the increase in the number of chronic diseases and “illnesses” of the current era (20).

It is known that whole grains are rich source of fiber, minerals (Mg, K, phosphorus, Se, Mn, Zn and Fe) vitamins (specially, B complex and E), phenolic compounds, phytoestrogens (lignans), and related antioxidants. By the fact that these diets are relative low in both dietary fibre and starchy staple, it is accepted that food processing leads to low chewing forces and weak jaw muscles that result in inadequate jaw growth and a high frequency of formerly rare mal occlusions and impacted teeth (171).

1 | MAJOR DIETARY AND PHYSICAL ACTIVITY TRANSITIONS

There are seven major recognized dietary changes (25). From paleolitical to western-modern nutrition, we have shifted our dietary macronutrient composition toward carbohydrates at the expense of protein, increased the intakes of ω6 fatty acids (notably LA from refined seed oils), SAFA and industrially produced trans fatty acids, decreased our ω3 fatty acid intake (both ALA and those from fish oil), shifted to a carbohydrate-rich diet that contains a high percentage refined carbohydrates with high glycemic indices (e.g., highly processed grains, sucrose, fructose), decreased the intake of certain micronutrients (e.g., folate, vitamin D, magnesium, zinc), shifted toward acid-producing foodstuffs (like meat, grains) at the expense of base-producing counterparts (fruits, vegetables), increased our sodium (salt) intake and reduced our potassium intake, and decreased the intake of fiber (25).

In the past 100 years, not only food intake, but also physical activity patterns have changed drastically in Western countries. Concomitant with this shift in energy metabolism, the incidence rates for obesity, type 2 diabetes, cardiovascular disease, hypertension and other life style- associated pathologies have reached epidemic (172,173). Thus, in contrast to the previous 250,000 years when Homo sapiens mainly struggled with a lack of food, we now pay the price for an abundance of energy-rich food and the decreased importance of physical activity in daily life (174). Obesity, sarcopenia and osteoporosis are major global health problems with an increasing prevalence and high impact on mortality and morbidity.

THE FRUGALITY OF THE THRIFTY GENOTYPE IN AN UNFAVORABLE ENVIRONMENTAL CONDITIONS

According to the frugal gene theory, proposed in 1962, genetic characteristics that prove to be advantageous in some way would be maintained in a population through a process of positive selection (26). Genetic traits may be positively or negatively selected relative to their concordance or discordance with environmental selective pressures. When the environment remains relatively constant, stabilizing selection tends to maintain genetic traits that represent the optimal average for a population .

When environmental conditions permanently change, evolutionary discordance arises between a species' genome and its environment, and stabilizing selection is replaced by directional selection, moving the average population genome to a new set point. Initially, when permanent environmental changes occur in a population, individuals bearing the previous average status quo genome experience evolutionary discordance.

In the affected genotype, this evolutionary discordance manifests itself phenotypically as disease, increased morbidity and mortality, and reduced reproductive success. In conjunction with this discordance between our ancient, genetically determined biology and the nutritional, cultural, and activity patterns in contemporary Western populations, many of the so-called diseases of civilization have emerged (25).

1 | THE CHOLESTEROL-RELATED DISEASES

Blood cholesterol elevation was one of the first risk factors identified for vascular disease (175)apolipoprotein (apo and is being considered as an Alzheimer risk factor. Alzheimer risk increases in association with high consumption of animal fat. In particular, cholesterol consistently increases the accumulation or production of the Aß-peptide, which is strongly implicated in Alzheimer's disease (176–178).

It has been described that cholesterol content of cell membranes affects the extent of oxygenation. In this sense, the cholesterol content of red blood cell membranes affects the extent of oxygenation of hemoglobin. Consequently, patients with high blood cholesterol levels have less oxygenation. In the same sense, cell mitochondria has the lowest cholesterol content of any eukaryotic organelle (179), which may relate to its prokaryotic (i.e., cholesterol-free) origin. Then, cholesterol accumulation in mitochondria membranes will decrease the organelle oxygenation and cell aerobic capacity and, therefore, an increased damage caused by cardiomyocyte ischemia, as experienced during chest pain (104). As in the case of heart disease, cholesterol and oxygen may also have implications for cancer research, again involving the mitochondrion (180). Increased mitochondrial cholesterol levels, possibly

by inhibiting oxygen entry into the mitochondria, reduces oxidative phosphorylation (181). Unlike normal cells, cancer cells shun mitochondrial oxidative phosphorylation in favor of glycolysis. This altered mode of energy generation apparently gives cancer cells a survival advantage. Viruses like yellow fever and dengue fever or the parasite that causes malaria seem to need cholesterol for invading the organism and reproducing.

Similar to high-plasma cholesterol, reduced plasma cholesterol also is associated with abnormalities. Disturbances in cholesterol synthesis, either caused by genetic lesions or pharmacologically, tend to be associated with increased cataractogenesis (104).That is because the fiber cells that comprise the lens are especially rich in cholesterol and, the fiber cell's high cholesterol content may also limit oxygen entry. These cells are packed into a honeycomb-like array, a regular arrangement that confers ideal optical properties to allow efficient transmission of light, and is partially maintained by the high cholesterol content of the plasma membrane (115). Lower cholesterol content in the fiber cells could damage intracellular lens proteins contributing to cataract formation. Ultraviolet radiation, oxygen, and perturbed cholesterol metabolism in the lens can converge to precipitate cataracts (104).

There is a compelling body of evidence that there is no net or even bidirectional, movement of cholesterol from plasma lipoproteins across the endothelial cells of the blood-brain barrier to the cells of the CNS. Only 6-8% of brain cholesterol comes from the diet. Therefore, essentially all cholesterol required for myelin formation in these cells came from brain endogenous synthesis and not from exogenous, lipoprotein cholesterol. Furthermore, indirect evidence suggests that large amounts of cholesterol turnover among the glial cells and neurons during brain growth and neuron repair and remodeling. This internal recycling of sterol may involve ligands such as ApoE and ApoAI, and one or more membrane transport proteins such as members of the LDLR family (105). Therefore, changes in cholesterol balance across the whole body may, in some way(such as by using drugs), might cause alterations in sterol recycling and Apo E expression within the CNS, which, in turn, may affect neuron and myelin integrity (86).

2 | THE FRUGALITY OF ABCA1 MUTANT

The ATP-binding cassette transporter A1(ABCA1) plays a key role in cholesterol efflux and transfer from peripheral cells to lipid-poor apolipoprotein A1 (ApoA1), the first step in HDL particle formation (182,183).

A gene variant (R230C, rs9282541) was associated with low high-density lipoprotein cholesterol (HDL-C) levels (184) because the genetic variation affects the gene ABCA1 (packaged in chromosome 9) and leads to alteration of a protein in the cell membrane that controls the level of cholesterol in the cells. The mutation increases the energy reserve of

cells, which is fundamental in periods of food scarcity, like those which the first inhabitants of America – and other parts of the globe – must have frequently faced before agriculture became stabilized and animals were domesticated (185).

As a result, the cells accumulate 30% more cholesterol and, the reduction in cholesterol flow out of the cells. Consequently. cells with the altered form of the gene liberate 30% less cholesterol into the bloodstream. It is known that viruses like yellow fever and dengue fever or the parasite that causes malaria seem to need cholesterol for invading the organism and reproducing. Hence, with less cholesterol at the disposal of the infectious agents, more people would survive and would transmit the altered gene to future generations. The peoples in whom the mutation in the ABCA1 gene mutation is most common live in regions with the greatest incidence of these infections. Thus, the mutation must have favored the survival of individuals because its effect was to protect them against infectious diseases. “In times like these, up to 80% of the people who survived were likely to be carriers of at least one copy of the altered form of the ABCA1 gene (185).

From Asia, Europe and Africa population data, it was found that the alteration in genetic ABCA1 does not exist on other continents than American peoples and affects, on average, 15% of native Americans. The distribution of this genetic variation is more homogenous in Mexico and Central America, low in the Andes and oscillates in the lowest lying lands in South America. It is estimated that the variant that favors the accumulation of cholesterol in the cells appeared 8,300 years ago, almost 10,000 years after the first human beings arrived in America. This date coincides with that of the domestication of corn and strengthens the idea that the cereal may have contributed to the positive selection of this mutation (183).

The wild ancestor of corn, a grass called teosinte, started being cultivated 8,700 years ago in in southern Mexico, where it is estimated had been the source of 70% of the calories consumed by the peoples of Mesoamerica and is still the basis of the region’s diet, have been found there. Therefore, it is reasonable to think that the start of agriculture in America had an influence on the selection of the mutated form of ABCA1.

Concurrently, archaeological information suggests that periods of famine (and high mortality) were frequent in the first few thousand years before production became stable. Only those who managed to store energy and support their hunger for longer would be capable of getting through these periods (185).

2.1 ABCA1 Mutants on Modern Environment

Counteracting its fundamental role in periods of food scarcity it was seen that among the known alterations of ABCA1 are the one that contributes most to reducing HDL levels, the most common form of dyslipidemia in Mexico. In fact, the reduced levels of HDL cholesterol was found in 20% of those with ABCD1 mutation, more common among obese

people, who have diabetes and abnormal levels of cholesterol (dyslipidemia). This follows the suggestion that genetic susceptibility of Hispanics to type 2 diabetes (T2D), obesity and dyslipidemia is related to their Native American heritage (184,186,187).

Thus, for almost 300 generations, cells have housed a genetic alteration that in the past allowed them to survive, but over the last 40 years has been contributing to ill health. That is because at times of plentiful calories, the mutation favors the development of the health problems that are growing fastest in the world: obesity, diabetes and the cardiovascular diseases. Whatever the explanation, it is certain that the factor that allowed people to get through times of hunger today adversely affects the health of Amerindians (185).

3 | THE FRUGALITY OF THE ALLELE APOE-4

ApoE plays a critical role in regulating the uptake of cholesterol and lipids throughout the body (188).

The comprehensive analysis of haplotype diversity showed that ε 4 is the ancestral APOE allele in humans, and the divergence of the ε 4 and the ε 2 and ε 3 clades occurred between 200 000 and 300 000 years ago (189). Our chimpanzee-like ancestors had a monomorphic APOE allele that is thought to be functionally similar to humans' ε 3 allele (190). Therefore, the ε 4 allele was an evolutionary novelty during human evolution (190).

The evolution of the unique E3 allele in Homo at the apolipoprotein E (apoE) locus was important for allowing our ancestors to exploit diets with greater animal material while, ApoE2 is most common in the Mediterranean basin where agriculture is thought to have begun (98). Therefore, some have suggested that APOE ε 4 evolved in response to shifts in diet ('a thrifty gene'), allowing for fat accumulation when nutrition access fluctuated (191–193). Thus, ApoE4 (the ancestral lineage) represents a more lipid-thrifty variant that is more efficient in sequestering cholesterol and has been better maintained in populations with a tenuous dietary supply such as in neolithical (193). Consequently, the ε 4 allele likely evolved in response to selection pressures early in our evolutionary lineage. Therefore, among the candidates for thrifty genes is the apoE4, whose geographical distribution has been linked to a possible thrifty role in lipoprotein and cholesterol metabolism (194).

3.1 Human Migrations and ApoE Alleles

Today, the frequency of the ε 4 allele in human populations around the world, generally follows a U-shaped latitudinal gradient, with the highest frequencies (up to approximately 40–50% of the population) in equatorial and high latitudes, and lower frequencies in middle latitudes (192,195).

Beginning approximately 2 million years ago, our ancestors moved into more open

environments and likely lost body hair to improve thermoregulation through sweating (196). At this time, melanin-rich skin evolved to protect the subdermis from the damaging effects of ultraviolet (UV) radiation, especially on blood folate levels, which are essential to fetal development. However, melanization also inhibits vitamin D synthesis (197). Thus, the original evolution of the ε 4 allele from the isoform present in our last common ancestor with chimpanzees may have allowed for highly melanized skin to protect blood folate, and still permit the absorption of vitamin D (198).

On the other hand, human migrations north into Europe and Asia, likely between 200 000 and 500 000 years ago, led to reduced levels of UV radiation and lighter skin colors (197). For a given dose of UVB radiation, lighter skin color leads to relatively higher levels of vitamin D synthesis compared with darker skin colors (199). Thus, with the evolution of lower levels of melanin in the skin, it is possible that selection for vitamin D synthesis and uptake was relaxed, allowing for the evolution of APOE ε 2 and ε 3 isoforms (198).

3.2 ApoE-4 Allele and Vitamin D status

It is suggested that the ε 4 allele leads to greater intestinal absorption and renal reuptake of vitamin D. Therefore, human ε 4 carriers had significantly 13-25% higher levels of vitamin D compared with ε 2 and ε 3 carriers (200). Hence, selection likely acts strongly to regulate vitamin D status due to the foraging.

Thus, among the proposed several possible scenarios for the evolution of the ε 4 allele, there is a suggestion that the ε 4 allele evolved to protect against vitamin D deficiency (191,200,201). Based on the benefits of ε 4 to support higher vitamin D levels, it is suggested a possible evolutionary scenario that can account for both the evolution of ε 4 from our last common ancestor with chimpanzees, and the current latitudinal gradient of ε 4 prevalence (192).

3.3 ApoE-4 Allele and Reproductive Function

Deleterious effects of low levels of vitamin D, include impaired reproductive function, increased risk of infections, rickets, and cardiovascular disease (202).

The selection effect on Impaired Reproductive Function may be mediated through the fact that the apoE4 variant favors steroid genesis and hence fertility (203,204). In support of this argument it has been shown, in a random sample of post-menopausal women, that carriers of apoE4 had more children than women with apoE2 (203). The Frisch (1982) (205) hypothesis is that occurs a suppressed fertility during times of maternal energy depletion. In Bangladesh and in Gambia, the lowest birth rate falls exactly 9 months after the time of greatest maternal weight loss during each year's hungry season. Thus, it was shown the very strong seasonal variation in birth rates in two populations exposed to seasonal agricultural patterns.

3.4 ApoE Alleles and Human Lifespan and Longevity

Humans live longer than any other primate, and are unique in having a prolonged post-reproductive lifespan (191,206,207). Despite some uncertainty over the timing of old age, the early evolution of longevity (approximately 1.8 million years ago) with H. erectus is most consistent with hypotheses for the evolution of the post reproductive lifespan that link successful aging to the origins of hunting and gathering (206–208).

Growth and development data from H. erectus (timing of third molar eruption and growth of body and brain size) suggest a lifespan of 60 years (196,209,210), a major jump over earlier species (e.g., species of Australopithecus) with estimated lifespans of 30 or 40 years. Most hypotheses for the evolution of human longevity (e.g., the 'Grandmother hypothesis') are centered on the ability of post-reproductive individuals (grandparents) to aid their offspring and their offspring's children, thereby improving their own reproductive success (206,207,211,212). As counterpart, the increased lifespan, and high levels of function in the elderly, would have enabled older adults to assist younger kin, reinforcing the selective benefits of old age (207,208,211).

It is well established that human aging today is characterized by substantial heterogeneity, often expressed as a continuum that can extend from successful to pathological aging (213,214).

Among the many hypotheses of evolving human longevity (206,207,211), a series of classic articles (98,191,201,215) argued that the evolutionary origins of the long human lifespan are tied to the interaction between diet and genotype. For though, the later evolution of ε 3 and ε 2 alleles, may have paved the way for further increases in lifespan evident in Upper Paleolithic human populations and modern humans (98,191,215). In fact, it is argued that humans' exceptionally long lifespans are a product, in part, of the evolution of the ε 3 allele, especially because diets shifted to include more meat and increased dietary fat and cholesterol later during our evolutionary history (98).

3.5 ApoE-4 Allele and Elder-Human Diseases

Humans have exceptionally long lifespans compared with other mammals and, our longevity evolved when our ancestors had two copies of the apolipoprotein E (APOE) ε 4 allele, a genotype that leads to a high risk of Alzheimer's disease (AD), cardiovascular disease, and increased mortality (198). In fact, specifically, carriers of the ε 4 allele of the APOE gene (responsible for lipid transport) have higher levels of total cholesterol and accumulation of atherosclerotic plaques in arteries, leading to increased risks of cardiovascular disease and stroke, as well as dementia and AD (189). The APOE ε 2 and ε 3 alleles confer reduced risks of these diseases of aging relative to the ε 4 allele, and are relatively recent additions to the human genome, with the ε 3 and ε 2 allele clade having evolved by 200 000 years ago (189). Today, prevalence of these alleles varies around the

world, but in most populations, ε 3 is found in the highest frequency (mean = 78.3%; range: 8.5–98.0%), followed by ε 4 (mean = 14.5%; range: 0–49.0%), and ε 2 (mean = 6.4%; range: 0–37.5%) (192).

3.6 Effects of Physical Activity in Relaxing ApoE-4 Actions

The evolutionary history of the APOE gene presents a vexing paradox. As described, data suggest that lifespans began to increase before the evolution of ε 2 and ε 3. In this context, how did selection generate longer human lifespans when all individuals had two copies of the deleterious ε 4 allele? Analyses of paleolife-history suggest (by the fossil record) that the long post reproductive lifespan of humans, began to evolve in concert with the shift towards higher aerobic activity in H. erectus , when the only available APOE allele was ε 4. It is suggested that this shift to higher levels of physical activity during human evolutionary history relaxed APOE-related constraints on lifespan as far back as 1.8 million years ago, though relaxing disease-related constraints on the evolution of humans' uniquely long lifespans. This hypothesis for the evolution of the human lifespan shows how increases in aerobic activity during our transition from a low-activity, sedentary, apelike lifestyle, to a high-activity hunter-gather lifestyle served to relax constraints on aging imposed by the deleterious homozygous APOE ε 4 genotype.

From neuroscience, anthropology, and brain-imaging research, it is proposed a hypothesis that the evolution of increased physical activity served to reduce the amyloid plaque and vascular burden of APOE ε 4, relaxing genetic constraints on aging. The overall hypothesis is that aerobic physical activity had an essential role in the evolution of human aging and longevity (198).

Physical activity seems to diminish CAD risks in APOE ε 4 carriers to ε 4 non-carrier levels, whereas sedentary lifestyles may exacerbate CAD risk factors among ε 4 carriers (216,217). In a cross-sectional study, ε 4 carriers showed a significant protective effect of high-intensity activity, with athletic ε 2, ε 3, and ε 4 carriers having similar blood lipid profiles and sedentary ε 4 carriers showing significantly high levels of lipid risk factors for CAD (216). A similar result was found in a cross-sectional study of middle-aged highly fit and age-matched sedentary groups, where inactive ε 4 carriers had elevated risk factors of CAD, including higher circulating LDL levels compared with physically active ε 4 carriers, and compared with ε 3 carriers regardless of aerobic activity levels (217).

3.7 ApoE-4 on Modern Environment

Evidence suggests that increases in the human lifespan began as early as 1.8 million years ago (208), when our ancestors were likely homozygous for APOE ε 4. In an evolutionary context diseases such as CAD, AD and other age-related dementias, may be due, in part, to the mismatch between our genetic heritage and our modern environment. In fact, changes induced by modern-day environmental constraints and human behavior may

have led to greater vulnerability to the effects of APOE ε 4 in subgroups of elderly in which high levels of physical activity throughout life are no longer required. Without a continued lifestyle of high physical activity, regions of the world where the ε 4 allele remains highly prevalent (e.g., equatorial Africa with ε 4 frequencies approaching 50%) may experience a substantial increase in CAD, AD, and dementia with the increasing globalization of sedentary lifestyles. Brain function as measured by functional MRI also interacts with genetic risk for AD and exercise status (218). Exercise appears to improve brain aging in individuals carrying the ε 4 allele. These were demonstrated either by cross-sectional as by longitudinal studies (216,217,219,220).

Longitudinal studies suggest that physical inactivity leads to increased risk of developing dementia or AD in APOE ε 4 carriers (220). While mid-life exercise generally reduces the risk of developing AD or dementia in all subjects, carriers of the ε 4 allele who participated in higher amounts of mid-life leisure-time exercise had greater protection against dementia or AD approximately 20 years later compared with ε 4 noncarriers (219,220).Thus, the genetic risk imposed by the ε 4 allele may be particularly high among individuals leading sedentary lifestyles, with physical activity equalizing disease risk among all genotypes. The above evolutionary hypothesis sheds important light on current ideas for prevention of CAD and AD (198).

Although the possible hypotheses for the early evolution of the ε 4 allele have been suggested, it is important to note that our overall conjecture that the evolution of increased aerobic activity relaxed a constraint on aging in our ancestors having the ε 4 allele does not specifically depend on the vitamin D or other explanations for the early evolution of the ε 4 allele (198).

4 | THE MISMATCH OF ANCESTRAL GENOME WITH THE CONTEMPORARY BEHAVIOR

Approximately 30 years ago in a series of studies Backer et al. (1989) (221) and Hales et al. (1991) (222) have shown that men (at age of 64 years) with (recorded) lower birth weight and lower weight at 1y of age had the highest death rates than did those of normal birth weight. From those data they established the concept of metabolic programming during early life. Interactive effects of birth weight and current weight may vary by disease outcome such as blood hypertension (223), insulin resistance (224,225) diabetes (226,227) plasma cholesterol, triglycerides markers of inflammation and CVD (65). Additionally, there is a close correlation between nutrition and the recent exponential increase in the conditions of obesity (19), dyslipidemia (86), diabetes (57), hypertension (21), metabolic syndrome (35) and cardiovascular disease, as seen in nations who adopted the “western lifestyle”. Thus, as our civilization evolved, a sedentary lifestyle and sodium- and energy-rich diet, the thrifty genotype is no longer advantageous, and may be maladaptive to disease phenotype,

such as hypertension, obesity and insulin resistance syndrome (117).

4.1 Obesity

Mammals have evolved mechanisms to store energy as fat during periods of plenty, which helps to guarantee survival during periods of drought and famine. According to this paradigm, a gene or a set of gene predisposing to obesity presumably evolved owing to a selective advantage in ancestral "feast and famine" environment and remained in polymorphic state in the population. The thrifty gene was under positive selection pressure in ancestral life when seasonal and climatic conditions resulted into fluctuating food availability.

Epigenetically hyperadiposity is resulted from the expression of genes favoring the storage of excess calories as fat that becomes maladaptive in a rapidly changing environment that minimizes the opportunities for energy expenditure and maximizes the opportunities for energy intake. Hence, the thrifty gene hypothesis suggests we evolved genes for efficient food collection and fat deposition to survive periods of famine and now that food is continuously available, these genes are disadvantageous because they make us obese in preparation for a famine that never comes. Hence obesity would be consequence of an adaptive response to our thrifty genes selected naturally from adverse ancestral scenarios. This genotype is turning pathological in the modern urban environment selectively affecting individuals with the gene(s) (19).

In their conceptual article Hales & Barker (1992) (228) proposed in the thrifty phenotype hypothesis that small human neonate represents a survival phenotype with a number of characteristics that increase its likelihood of immediate survival after poor nutritional experience in uterus. They postulated that under conditions of suboptimal in utero nutrition, the fetus must adapt to its environment to ensure survival of the organism, through a "sparing" of vital organs such as the brain at the expense of organs such as pancreas, kidney and skeletal muscle. It was proposed that a metabolic programming occurs to promote nutrient storage to provide a survival advantage in conditions of poor post- natal nutrition (229). However, variation in early life experience (metabolic programming) has many consequences in late life. For example undernutrition in utero increases the risk of NCDs in adulthood (80,81). In fact, these (mis)adaptations can lead to the post natal development of obesity, T2DM, blood hypertension, dyslipidemia and metabolic syndrome in conditions of adequate nutrition or overnutrition (18–20). Many epidemiologic studies in populations worldwide have robustly supported the initial findings that poor fetal growth resulting in low birth weight increases the risk of developing diseases in adulthood (230). Therefore, the thrifty phenotype hypothesis is widely used to interpret associations between early nutritional experience and degenerative disease risks (65).

Regarding these ancestral genoma, it seems that our genetically determined "survival strategy" turns against us now that we can eat whatever we want and whenever

we want, and need little physical activity for food procurement. This, so-called obesogenic environment has never existed in the past, was consequently not part of selection pressure, and genetic adaptations might therefore also not be expected. Consequently, obesity is not a genetic disease, apart from some rare mutations (231).

Shortly after the end of World War II, an unprecedented environmental change took place in the western part of the globe. For the first time in human experience, the eating habits entire nations were altered by the marketing of processed food having in common a high carbohydrate and fat content, very low cost, and easy availability in supermarkets and fast-food restaurants. The aggressive promotion of these foods, coupled with a reduction in caloric expenditure resulting from new immobilizing technologies, changed the caloric balance of at least two generations of people (232). Moreover, there has been a decreased health consequences resulting from obesity by bringing a host of new drugs and devices to the market to better manage the adverse health effects that obesity promotes. Thus the changing obesogenic environment is widely in response to consumer's demand for labor saving technology and convenient, affordable food (233).

The conclusion that obesity is "caused by an interaction between genes and environment" distracts from its causation by our current "faulty" environment and therefore does not carry useful information from a public health perspective. The identification of the underlying genes is nevertheless important from the point of view of health care, since it may help us target treatments in those who have developed disease from underexposure or overexposure to the underlying environmental factor(s) (99).

4.2 Type 2 Diabetes

Paleolithic nutrition is virtually devoid of high–glycemic index carbohydrates (234). Hence, it has been proposed that insulin resistance has evolved as an adaptation to relatively low carbohydrate foods consumed by our ancestors for millions of years, along with higher physical activity (235). Relative insulin resistance evolved to aid metabolic partitioning between physical activity and other functions during constrained energy supply (148), which in turn relate to the selective pressure of a low glycaemic load diet with high meat content as our gather-hunter ancestors use to eat over ten thousand years ago. In this sense, T2DM is considered a thrifty phenotype exceptionally efficient in the intake and utilization of food with basic difference of a quick insulin trigger in response to food-induced hyperglycemia. This would lead to the more efficient utilization of food and tissue distribution of plasma glucose. The survival benefit of this phenotype was to minimize urinary glucose loss when fasting was promptly replaced by feasting (20). Further on, the agricultural revolution yielding carbohydrate-rich crops as staple foods relaxed the selection pressure. The subsequent industrial revolution enabled the skyrocketing of agricultural production, which provided a continuous (over)supply of calories for every society member for the first time in human history. Moreover, food processing introduced massive amounts of simple

carbohydrates into our dietary repertoire. Although myriad signs indicate that our gene pool rapidly adapts to the novel nutritional environment many of us still carry gene variants that promote insulin resistance (236).

4.3 Essencial Blood Hypertension

The evolution of genetic susceptibility to hypertension is ancestral and, has been hypothesized to begin in Africa by the carriers of the (salt-sensitive)sodium-conserving (thrifty) genotype. However, the natural selection of thrifty genotype, which was a physiological adaptive mechanism for human survival, when on the current environment, is maladaptive to disease phenotype (21). In fact, this phenotype may be maladaptive to the modern environment of sodium abundance (128). Additionally, insulin increases sodium reabsorption in the kidney and promotes sympathetic nerve activity, Then, hypertensive patients with salt sensitivity are more insulin resistant than those with salt-resistance (117). Thus, high salt diet impairs insulin sensitivity only in hypertensive patients with salt sensitivity but not in those with salt-resistance, suggesting that there is a pathogenic link among hypertension, salt- sensitivity and insulin resistance (21). Furthermore, in the state of insulin resistance, the insulin- stimulated nitric oxide (NO) pathway is selectively impaired and the compensatory hyperinsulinemia may activate MAPK pathway, resulting in enhancement of vasoconstriction, pro- inflammation, increased sodium and water retention and the elevation of blood pressure (237). Hence, vascular deleterious effects of insulin resistance include induction of vasoconstriction and pro-inflammatory activity (21).

Thus, hypertension comes out as a mismatch between our ancestral genome with the current western lifestyle. With the switch to a sedentary lifestyle and sodium- and energy-rich diets (current obesogenic environment), the thrifty genotype and ancient frugal alleles, are no longer advantageous, and may be maladaptive to disease phenotype, resulting in hypertension, obesity and insulin resistance syndrome (21). The coexistence of insulin resistance and hypertension results in a substantial increase in the risk of developing cardiovascular disease and type 2 diabetes (65,121). The underlying mechanism is complex and may involve a low grade chronic inflammation and oxidative stress (238).

5 I RESISTANCE OF PATHOGENS TO ANTIBIOTICS

The interface of evolutionary biology and medicine understood that “humans coevolved with a normal community of symbiotic and parasitic microorganisms” and, from the progress of this interface, we have learned that pathogens evolve much faster than we do, so infection is unavoidable. That is because pathogens rapidly evolve resistance to antibiotics and, pathogens evolve strategies to circumvent host defenses, and the virulence levels are shaped by natural selection to maximize transmission.

Similarly to the evolved resistance of pathogens to antibiotics, cancers rapidly

evolve resistance to chemotherapy. Thus, far from suggesting quick new cures, the general messages of Evolutionary Medicine help to explain why disease is so prevalent and difficult to prevent (27).

The main lessons taken through evolutionary medicine would be:

a) Humans coevolved with a normal community of symbiotic bacteria and parasitic worms; when they are eliminated by either hygiene or antibiotics, our immune systems can react to this unnatural situation by producing allergies, asthma, and autoimmune disease, including very serious ones like Crohn's disease, which can be treated by ingesting eggs of parasitic worms (239); b) By receiving more antibiotic treatments than average before 2 years increases the risk of obesity and allergies (240,241); c) The widespread use of imperfect vaccines, vaccines that do not completely and permanently eliminate the pathogen from the body of the person vaccinated, could lead to an increase in the virulence of the pathogen (242); this is of particular concern in the case of malaria vaccines (243). These insights illustrate how evolutionary thinking on medical issues can sometimes illuminate features quite unexpected by non-evolutionary approaches (27).

EPIGENETICS OF NCDS

The Evolutionary Medicine establishes as general message that, the idea that common heritable diseases are caused by a few defective genes is usually incorrect (14). An evolutionary view suggests that many genetic variants interact with environments and other genes during development to influence disease phenotypes. Epigenetic changes are defined as mitotically inheritable alterations in gene expression that are not related to changes in DNA sequence. There are at least two distinct mechanisms through which epigenetic information can be inherited: histone modifications and DNA methylation (244).

Epigenetic modification of gene expression is one mechanism by which genetic susceptibility and environmental insults can lead to mostly of the contemporary NCDs. “One of the most important influences affecting genetic selection and adaptation is the interaction between a species and its food supply” (245).

It is noteworthy that disruptions of the equilibrium achieved in evolutionary conflicts of interest among relatives may be the basis of some mental diseases, particularly autism and schizophrenia (246). In line with the view that “Medicine needs evolution” (15), because “Nothing in medicine makes sense, except in the light of evolution” (41), two correlated hypotheses have been advanced (247,248). These hypotheses inspired by evolutionary theorizing, which “points to hypotheses that we otherwise might not even think of” (249), are based on the idea that evolution adapted genetically the metabolic physiology of our ancestors to cope with sugar only in diluted forms, because prehistorically diluted sugar was available abundantly in fresh fruits but undiluted sugar was inexistent (247,248). Those hypotheses (247,248) posit that evolutionarily conserved physiological traits make diluted sugar harmless and undiluted sugar harmful.

FUTURE DIRECTIONS

In the end, our understanding of human evolutionary history can help inform on how we should proceed from both a local and a global health perspective today, suggesting research directions leading to public health policies to support successful aging in older populations worldwide. This multidisciplinary approach links human evolution with health and provides a complementary perspective on aging and neurodegenerative disease that may help identify key mechanisms and targets for intervention. Thus, the context of human evolutionary history serves as a foundation to further advance multidisciplinary efforts toward unraveling the mechanisms behind exercise-induced neuroprotection and increased longevity with successful aging, while helping to identify those who may benefit most from exercise interventions (198).

1 | PHYSICAL ACTIVITY-APOE-4 INTERACTION

If longevity evolved in humans to, in part, allow grandparents to aid offspring in raising grandchildren, then we must understand how our ancestors aged successfully despite being homozygous for APOE ε 4. To understand how the long human lifespan evolved within this constraint, it is important to view lifespan evolution within the context of aging outcomes that we see in living humans. Variation in human aging today is often expressed as a continuum that ranges from successful aging, having a long lifespan with high levels of cognitive and physical function, to pathological aging with impaired cognition and diminished physical capacities that can lead to dementia and relatively increased mortality (213,214).

Studies suggest that lifestyle factors, specifically aerobic exercise, can have a positive impact on the aging brain, as well as physical longevity, especially in carriers of the ε 4 allele (218,219,250). Here, we argue that aerobic physical activity had an important role in the evolution of the human lifespan before the origins of the ε 2 and ε 3 alleles. The review of the evolutionary links between physical activity, brain aging, and longevity are especially timely given the intense research focus on the use of exercise to reduce risks of developing disorders such as cardiovascular disease, AD, and other age-related dementias, including vascular dementia (218).

Regarding the brain functions, odds ratios for cognitive decline are significantly higher among ε 4 carriers who exercised for less than 1 h per day over 3 years compared with ε 4 carriers who exercised for more than 1 h per day (250). In some studies, engagement in physical activity seems to reduce risks of cognitive decline in ε 4 carriers only (251), whereas others have found that physical activity reduces risk of AD in ε 4 carriers, but has a similar reduction in dementia risk for all genotypes (252). Thus, in studies with high quality measures of physical activity, there is clear and growing support that engagement in

physical exercise has a protective effect for APOE ε 4 carriers (198).

APOE ε 4 carriers who were physically active also had a lower probability of cognitive decline compared with less active ε 4 carriers (251). Finally, in homozygous ε 4 women, cardiovascular fitness was positively correlated with performance on a series of cognitive tests (253).

Among the mechanisms behind the protective effects of exercise on pathological brain aging there are indications of enhanced neurogenesis (254), showing that exercise and physical activity may reduce amyloid deposition in the brain, a key marker of AD pathology (255,256). Regarding the potential interaction between APOE genotype, physical activity, and brain structure, several studies have found evidence that, without taking genotype into account, physical activity and exercise can affect the volume of brain structures in both cognitively normal older adults, and in individuals with AD or dementia. Greater aerobic fitness in cross-sectional studies of older adults is associated with increased white matter tract integrity in the frontal lobes, temporal lobes, and the uncinate fasciculus and cingulum (257,258), larger gray matter volumes in temporal, parietal, and inferior frontal areas (259–262), and increased cortical, hippocampal, and whole-brain volume (263–265).

Intervention studies in aging cohorts found that several months of aerobic exercise can increase gray matter volume in the prefrontal cortex, lateral temporal lobe, and the hippocampus (260,266,267). In adults in the early stages of AD, aerobically fit subjects have larger total gray matter volumes, and greater volumes of the medial temporal lobe compared with less fit subjects (263,268).

Thus, there is growing evidence that physical activity, exercise, and aerobic fitness significantly reduce CAD risk and improve cognitive aging and biomarkers of AD pathology in APOE ε 4 carriers. Given the observed differences in brain function, structure, and connectivity, as well as reports showing the preferential build-up of Aβ in adult ε 4 carriers, it is possible that early or lifelong physical activity increases clearance of Aβ potentially through improved sleep or other mechanisms, and enhances brain resilience through neuroprotective processes, such as increased perfusion and neurogenesis. This hypothesis may provide an explanation for how the long human lifespan evolved despite the early high prevalence of the ε 4 allele (198).

In all cases, to contribute substantially to the well being and survival of younger kin, the evolution of the long human lifespan likely required older individuals to maintain high levels of both physical and cognitive health (198). From the present knowledge, our evolutionary heritage may help us tailor preventative interventions for individuals who have ancestral genotypes. These conclusions are important for populations around the world, where ε 4 allele frequencies can vary from <5% to nearly 50% (192).

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