Exploration of Medicine

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Determinants of human longevity: input of environment, nutrition, physical activity, eustress, heredity, health care, motivation, and mental state

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Academic Editor: Calogero Caruso, University of Palermo, Italy
Received: March 31, 2023 **Accepted:** July 31, 2023 **Published:** October 30, 2023

Cite this article: Zhdanov RI, Khayrullin RN, Khalilov RI, Eftekhari A, Sozinov AS. Determinants of human longevity: input of environment, nutrition, physical activity, eustress, heredity, health care, motivation, and mental state. Explor Med. 2023;4:755–71. https://doi.org/10.37349/emed.2023.00176

Abstract

The paper aims to review the possibilities of a complex transdisciplinary approach to forming health and longevity. Determinants of productive longevity (DPL) and health culture are reviewed; definitions of health, stress, and eustress, and their roles in active and productive longevity are given. DPL making a decisive contribution to the phenomenon of active longevity are stated and analyzed from the point of view of evidence-based medicine. They are as follows: 1) environmental factors including geographical location, "Blue zones", and mountain areas, as well as level of the environmental pollution; 2) dietary regimen to support active longevity, including vegetarianism, calorie restriction, fasting, the role of vitamins, biological antioxidants, geroprotectors, and micronutrients; 3) importance of activity and eustress phenomenon, by other words, lifestyle: physical activity, sexual relationship, Qigong and Yoga practices, cognitive activity, sense of humor, and acceptance of age in activities of daily living and survival; 4) genetic and epigenetic particularities as a condition for long-living; 5) level of health care and early diagnostics to prevent age-associated diseases; 6) the role of the state of mind and meditation as well, how it is used for forming health due to Qigong and Yoga natural systems, in religion, and medical practice; 7) motivation for active longevity that significantly increases chances to productive longevity.

Keywords

Human longevity, determinants, productive longevity, nutrition, heredity, physical activity, health care, motivation

Introduction

Topics and problems of health and active longevity are of great interest to people on all continents and at all times. Up to the present day, they are solved only for the limited number of long-livers, not many of whom are involved in cultural and industrial activity. It happens because human health is a complicated multifaceted category and has a form of an unbalanced biological and psychological natural system, still hard to understand [1, 2]. Although it is common to speak about the health of species, populations, persons, or families, in the article human health is considered at an individual level. Health represents an invaluable gift of nature, which almost everyone receives at birth, but people usually start to appreciate it when they face problems in their health. This is true up to the degree that almost on every grave it can be written: "He/she did not know how to live correctly and long". We primarily understand the culture of health as a part of general human culture, which is one of the main conditions of survival and tied to an attitude toward the health of both ourselves and others. Nations on the planet have various systems of health and longevity, formed at a certain time, and adapted to the conditions of their existence and national traditions [3–7]. Essentially all of these systems are transdisciplinary, as they combine traditional methods to preserve health, which are usually formed over centuries, as well as methods of modern medicine, which are now mostly disease-oriented and based on a pharmaceutical approach to disease treatment. However, at present only interdisciplinary and multidisciplinary approaches are normally used in formal health sciences.

Systems and regions of health and longevity

There are traditional phenomena and systems of health culture and longevity. They are commonly known and need to be discussed. To begin with, there would be mentioned the Chinese systems Qigong (traditional Chinese: 氣功) and even Dao Yin Yang Sheng Gong [5, 6], and the Indian ones: Yoga [7] and Ayurveda [8]. They have thousands of years of successful history behind them, emphasizing certain positions, movements ("those who move are healthier"), and meditation. Different definitions of health exist, the most widespread is given in the Preamble to the Constitution of the World Health Organization (WHO) [9]: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." It is supposed that if it is possible to live actively up to 80–85 years of age now, taking care of one's health using simple technologies, the result of their application will still be challenging if you do not have an answer to the question: Why do you need it? Only having answered this question, it is possible to decelerate the speed of aging. WHO did not leave people any choice, resolving that inhabitants of the planet are responsible for human health [10]. Health is determined as the wholeness of the organism enabling physical, mental, and emotional strain and relaxation afterward [11]. This definition itself implies a transdisciplinary approach to health. More specifically, consider not only interdisciplinary approaches (combination of physical activity with methods of physiologic diagnosis of heart rate variability) but use methods of several adjacent disciplines (multidisciplinary), for example, psychological diagnostics, giving information about the trait and state anxiety and coping strategy, as well as elements of Eastern practices. The aim of health support is active longevity, where everyone is capable not only of attending to self-care but also being of benefit to society, and where everyone is capable of living up to hundred years at least, in alignment with the concept of the death instinct (according to Goethe and Mechnikov) [3, 4]. Certain results and advances in the transdisciplinary approach to health-forming were demonstrated by microbiologist Mechnikov [3], engineer Mikulin [12], and engineer and cardiac surgeon Amosov [13]. Notably, both Mikulin and Amosov personally formed and exemplified the principles of health promotion, becoming long-livers.

A transdisciplinary approach to forming health and longevity should include practices and results from both Western medicine and nonconventional medicine (more precisely traditional medicine), in addition to the methods of evidence-based medicine. Currently, it becomes clearer that the classical Western approach to disease-oriented medicine, grounded on pharmaceutical medicine has run its course [10, 14]. The last one usually does not address the cause of disease, but it is aimed at the correction of symptoms and does not guarantee health to the general population [14, 15], and it is presumably successful in certain cases and for certain population groups. For this reason, some systems emerged, claiming to be an alternative treatment tied with the principles of evidence-based medicine to different extents, but sometimes far from them [14–17]. These books are likely fiction (as there are very few references to scientific sources), and are mentioned without further comments.

Aging biology and mechanisms

Basics and outlines of aging represent one of the central mysteries of biology. In 1825, Gompertz proposed an exponential increase in death rates with age [18]. The main statement quantifying human aging and mortality (and the most multiparous animals) is the Gompertz-Makeham law of mortality (the Gompertz distribution), which will reach its bicentennial milestone in two years [18]. According to the Gompertz-Makeham law, the probability of death in a fixed short period of time after age *x* is:

$\rho = a + b \cdot e^{cx}$,

where *x* is age, ρ is the relative probability of death over a certain period of time, and a, b, and c are constants.

This distribution is the sum of an age-independent component (the Makeham term) and age-dependent component (the Gompertz function). This law optimally describes the age dynamics of human mortality in the age window from approximately 30 years to 80 years and the decrease in population size with age. Death rates have been observed to increase at a slower pace. A detailed consideration of the applications of the Gompertz-Makeham law to biology and human lifespan situation has been conducted by Gavrilov and Gavrilova [19]. Since the article is aimed at the biology of aging and longevity, the first hypotheses and theories of aging will be discussed. There are many hypotheses of aging, but only some of them could be considered theories [20, 21]. In general, they focus either on neuroendocrine processes, genetic/epigenetic aspects, or evolutionary-ecological aspects of aging, and can be divided into the following groups with emphasis on: 1) a variety of age-related changes (so called stochastic aging) are associated with the accumulation of organelle, cell, and tissue damage, namely, due to free radical action (cell membranes, nuclei, and mitochondria); 2) genetics and epigenetics regulating gene expression, so aging-based processes can be genetically programmed or can be regulated through nucleotide methylation of functional genes; 3) a decrease in organism system reliability and associated decrease in regeneration and damage repair processes; 4) the substantiation of the evolutionary significance of aging processes.

The free-radical theory of aging was formally proposed by Harman in 1956 [22] and postulates that the inborn process of aging is caused by cumulative oxidative damage to cells by free radicals produced during aerobic respiration (the 1st group of hypotheses). Later, Harman modified his original theory into the mitochondrial theory of aging. This theory states that reactive oxygen species produced by mitochondria damage biological macromolecules—lipids, proteins, and mitochondrial DNA, which can lead to pathologies [23]. In the same field, Emanuel with colleagues worked for 30 years in the Institute of Chemical Physics at the Academy of Sciences of the Soviet Union in Moscow, the inhibitors of free-radical reactions—bioantioxidants being applied for increasing mice life expectancy [24]. They showed that bioantioxidants of low toxicity, which inhibit free radical processes, are anticarcinogenic, and data are given on their experimental utilization as possible 'geroprotectors' [25].

In 1973 Olovnikov [26] published a theory in which he first formulated the DNA end replication problem as the marginotomy hypothesis (the 2nd and the 3rd groups of hypotheses), and he explained how it could be solved. The solution to this problem also provided an explanation for the Hayflick limit, which underpins the discovery of *in vitro* and *in vivo* cell senescence. He proposed that the length of telomeric DNA, located at the ends of chromosomes consists of repeated sequences, which play a buffer role and should diminish in dividing normal somatic cells at each cell doubling [26]. After the exhaustion of telomers, the cells become aged and are eliminated due to the loss of some vitally important genes localized in end-replicons. Marginotomy is therefore responsible for the loss with age of various cell clones of the body, including some endocrine cell clones. Therefore, marginotomy may be the primary cause of various age-related disorders and the aging process of multicellular organisms [27, 28].

At the same time, Dilman [29] proposed the neuroendocrine theory (the 3rd group of hypotheses), which is based on the contradiction between homeostasis and development from juvenile to senile age. In this hypothesis, it is suggested that the key process in the genetic program of development and aging is a gradual elevation of the threshold of sensitivity of the hypothalamus to feedback suppression. This hypothalamic feedback provides stability to the internal environment in the developing differentiated organism. The elevation of hypothalamic threshold and the resulting rise in the activity of a number of hypothalamic centers lead to a compensatory increase in the activity of various peripheral endocrine glands. Later, based on this hypothesis, Dilman and his colleagues [30] proposed a neuroendocrine-ontogenetic model of aging and ways of its realization. The work on the theories of aging should ultimately be aimed at the elimination of diseases coupled with the mechanism of aging, slowing down the aging process, and broadening the human lifespan. There are two tendencies in treating the causes of disease development that can be readily traced. In the first one, the main emphasis is placed on external factors such as trauma, overnutrition and undernutrition, pathogenic microorganisms, viruses, chemical and physical carcinogens, stress, and so on. The second model of medicine deals with inborn genetic causes of the development of diseases or the predisposition to their development [30].

Although two main groups of theories claim to explain the biology and mechanisms of aging: 1) programmed aging (phenoptosis) which involves the launch of a self-destructive program within the human organism (the 2nd group of hypotheses) [31, 32] and 2) stochastic aging (the 1st group of hypotheses) [22, 25], there are other hypotheses (the 3d and the 4th groups) [33].

Now it becomes obvious that the development of civilization distances humans farther away from adequate "self-supporting" modes of life, accelerating aging [20, 21]. Three decades ago, one could propose a third option: aging in many species is not associated with a strictly programmed, nor a fundamentally stochastic mechanism; it rather results from their living under pessimal conditions [34]. Similar views about the decrease and full zeroing of the aging rate resulting from increased "pressure" of the environment keep appearing. This means that stochastic aging is likely to be a secondary phenomenon. But genetically determined phenoptosis does not necessarily have to be obligatorily constitutive. It may actually represent an inducible quasi-program of aging, which is triggered only when an organism leaves the area of self-sustaining modes of its functioning [35].

According to the regulatory-adaptive theory of aging by Frolkis [1970s, Kyiv, Ukraine Republic, Union of Soviet Socialist Republics (USSR)], human aging and life expectancy are determined by the balance of two processes [36]. Thus, along with the destructive process of aging, the process of "anti-aging" is unfolding in the human organism, which is named "*vitauct*" (latin: *vita*—life, *auctum*—increase). This process is aimed at maintaining the organism's reliability, its adaptation to the environment, and increasing life expectancy. For example, if the number of cell organelles mitochondria decreases with aging, then according to the *vitauct* phenomenon they increase in size and thus compensate for functionality [36].

Furthermore, recent studies in several different systems suggest that the rate of aging may not only be modified by environmental and genetic factors but also that the aging clock can be reversed, restoring characteristics of youthfulness to aged cells and tissues. The research efforts focused on the emerging biology of rejuvenation through the lens of epigenetic reprogramming due to defining youthfulness and senescence as epigenetic states (the 2nd group of hypotheses) [37].

It is also pointed out that the stochastic malfunctions of the mitochondrial electron transport nanoreactors, which produce the oxygen anion-radicals ($O_2^{\bullet-}$) as by-products of respiration, seem to be also of the first importance [38]. As a reducing agent, $O_2^{\bullet-}$ affects the nicotinamide adenine dinucleotide phosphate reduced/oxidized [NAD(P)H/NAD(P)$^+$] ratio and, by changing the activity of sirtuins, slows down the renewal of biomolecular constructs. As a consequence, the oxidative-stress products and other metabolic slag accumulate with the resulting impetus to autophagic or apoptotic cell death accompanied by age-associated clinical disorders. Thus, the free-radical redox timer serves as an effective stochastic mechanism of realization of the programmed deficiency in the reliability of biomolecular constructs (the 3rd group of hypotheses) [38, 39].

Gut microbiota plays a key role in aging-involved processes as a source of intestinal endotoxins [40]. It is elucidated that intestinal endotoxins of some gram-negative microorganisms represent not only aging markers but real acting inducers of aging and age-associated diseases, and endotoxin theory of aging was formulated [40–42]. The phenomenon of systemic endotoxemia [40] and the role of endotoxin-induced systemic inflammation in aging are consonant and in accordance with the "inflammaging" phenomenon reported by Franceschi and colleagues [43] and his hypothesis on the role of pro-inflammatory cytokines in aging. They consider low-intensive inflammation as a driving force of aging, and defined accelerated aging in an organism as a result of chronic inflammation factor accumulation [43, 44].

Wang and colleagues [45] summarized the data on increasing plasma levels of von Willebrand factor (vWF) with age. They point out that elevated vWF levels promote thrombosis, atherosclerotic plaque formation, inflammation, and proliferation of vascular smooth muscle cells. A non-cytotoxic dose of environmental pollutant cadmium (Cd) increases endothelial vWF expression and secretion *in vivo* and *in vitro*. They summarize the molecular mechanisms underlying vWF-promoted vascular aging-associated pathologies and Cd-induced vWF expression. The authors propose that exposure to low-dose Cd is a risk factor for vascular aging, through elevation of plasma vWF level [45].

There exists the phenomenon of successful aging as a result of increasing life expectancy in economically developed countries [46]. From this point of view, the Chinese health criteria for the elderly are intended to be comprehensive, relevant, and operational, whereas only such healthy longevity holds any significance [47]. They are composed of five categories, which contain varying numbers of items: 1) Major organs showing no functional abnormalities associated with aging; no major illness; risk factors controlled at levels considered satisfactory for the corresponding age group; possessing reasonable defense capabilities against disease. 2) Normal or nearly normal cognitive function; good adaptation to the environment; staying optimistic and proactive; satisfaction with life or positive self-evaluation. 3) Competent management of family and social relationships; active participation in family and social activities. 4) Self-sufficient or nearly self-sufficient in activities of daily living. 5) Normal nutritional status, appropriate body weight, and good lifestyle habits [47].

Determinants of productive longevity

What are the determinants of productive longevity (DPL) and super-longevity, and how do they contribute to it? For the discussion, it is conventional to estimate the contribution of these factors as follows [48–51].

Nature of living region and environment (and so called "Blue zones")

The role of regional and environmental factors is entirely evident and comprehensible. Areas with long-livers differ in their geographical position, they are mostly situated in validated "Blue zones" [52] or mountainous and seaside areas, but long-livers can be found sometimes even in cities [53, 54]. The state of ecology and level of environmental pollution is important in them. It was mentioned from the beginning China and India, where in certain regions long-livers and centenarians could be found, and their health systems Qigong and Yoga as cultural phenomena. To the east of China and India, another enclave of long-livers (90 years old and above) is situated on Okinawa Island in Japan (the first one of the validated "Blue zones" [55]), which was formed as a result of an advantageous combination of natural settings, customs, lifestyle, and nutrition [49–51]. The percentage of long-livers (90 years old) along with octogenarians (80–89 years old) and centenarians (above 100 years) is one of the highest there. There are only four more validated "Blue zones" along Okinawa Island on the planet: Ikaria, Greece; Sardinia Island, Italy; Nicoya, Costa Rica; and Loma Linde, the USA [52–54]. To the west of China (Tibet region), several well-known mountainous areas are located, where long-livers reside historically: Abkhazia, Georgia, Azerbaijan Republic (Caucasus mountains), and Iran (Talysh mountains) [56, 57] (see also https://testour.az/ru/blog/longevity-museum-in-lerik).

There is a magnificent combination of natural settings of a mountainous area (unique in terms of water composition of micronutrients and ionized air, rocks and gorges, and special geoelectromagnetic field). Despite the residents' strenuous work, whether in mountain mines or agricultural fields, they have access to ample vegetables and fruits, which plays a pivotal role in maintaining their good health. An elevated level of long-livers is also noted, e.g., in Nicoya on the Pacific Coast of Costa Rica at the isthmus between North and South America, and in other "Blue zones": Loma Linda, the USA, Ikaria Island, Greece, and Sardinia Island, Italy as well [53, 54]. There are some other not-validated regions related to officially validated "Blue zones" with an unusual number of long-livers, e.g., the Azerbaijan Republic and Iran at the Talysh mountains [56, 57]; Vilcabamba area in Ecuador; Martinique island [58] and other islands at the Caribbean Sea.

To summarize, despite there are geographical differences between all these "Blue zones" and related long-living areas, all these regions have a number of common features promoting active longevity. Mostly long-livers reside in isolated regions (it could be important to form genetic distinguishing characteristics), predominantly mountain areas with unique climate, water composition, atmosphere, and geophysical parameters (Okinawa Island, Sardinia Island, Ikaria Island, Vilcabamba, Caucasus and Talysh Mountains, including Lerik region). They appeared also in coastal areas with hard water, and rich with unique fruits (Okinawa, Ikaria, Nicoya, Loma Linde, and Martinica island [58] as well as other Caribbean islands).

Nourishment of long-livers is abundant in vegetables and fruits (often unique: papaya, avocado, mango, pineapple); and residents do not get ill. Long-livers typically consume low-calorie diet (calorie restriction: approximately 1,200 kcal or even less to approximately 800 kcal for elderly people), notably legumes (lentils, beans, corn, soybeans) have a special place in their nutrition. Moreover, they are enormously active physically, socially, and sexually, communicate with friends, and live in families. Their lives are filled with a sense (e.g., Ikigai custom in Japan) that gives them a feeling of responsibility and purpose even at the age of one hundred years. They have the right attitude to life, plant-based food, and vegetable garden pharmacy. They work usually in a garden, and consume a lot of soybeans, corn, nuts, and salad. In Tibet monasteries, for example, the food of monks is of the same type and fits in the palm. The resettlement to validated "Blue zones" (Okinawa Island, Japan; Ikaria, Greece; Sardinia Island, Italy; Nicoya, Costa Rica; Loma Linda, the USA) and related non-validated mountain areas (e.g., Vilcabamba, Caucasus, Caribbean islands) are popular nowadays, maybe also regarded as a transdisciplinary approach to form a culture of both current inhabitants and their descendants' health.

Nutrition (as a part of lifestyle)

As we have to take food regularly, its quantity and quality may have a decisive contribution to productive longevity. Although sharp qualitative changes are not noted in the structure of nutrition of long-livers, compared to the general population [2, 50, 51], quantitatively it is characterized by calorie restriction, reaching the minimum of approximately 800 to 1,200 kcal daily [59–61]. On the other hand, though their nutrition contains a lot of vegetables and fruits, including rare ones [62], no information is available about long-livers keeping to a raw or vegetarian diet. It should be noted, that nutrients would enter the body as part of the natural sources [63]. Studies of recent years with data analysis of 35,000 women aged 49 to 83 years showed that a popular trend of widespread intake of separated or synthesized vitamins or their complexes by population statistically increased the risk of cardiovascular and oncological diseases by 20–30% (http://dobroweb.ru/secrets/226). American Academy of Pediatrics, using the data of evidence-based medicine, has stopped recommending fruit juices for child nutrition in the first year of life since 2017, on the ground that their consumption increases risks of pathologies in mature age, particularly diabetes mellitus [64]. However, with advancing aging it is important to monitor the balance of micronutrients in nutrition, emphasizing essential micronutrients, in particular, zinc and selenium [65]. This conclusion relates to Blue zones, and for mountain areas, their long-livers reside at about 2,000 meters altitude, under the conditions of slight scarcity of oxygen, it could be noted that moderate anoxia and endogenic respiration of highlands residents are their common denominators.

Recently, much attention has been paid to the research of the human microbiome, in other words, the entirety of microorganisms living with humans in symbiosis [40, 43, 66, 67]. It appears to be a novel understanding of the role and importance of the microbiome and its endotoxins and the role of chronic inflammation as a system reaction. Now, it is considered that quietly smoldering chronic inflammation induces the development of almost all human age-associated pathologies, including cancer, atherosclerosis, neurodegenerative diseases, depression, and many others, endotoxins being not only markers of aging but act as inducers of aging [40, 42, 44].

Thereby, the works by Soviet physiologist Ugolev should be considered in the discussion of health issues, more specifically, the theory of adequate, related to species nutrition [68]. He was ahead of modern researchers, half of a century ago suggesting justifiably that food digestion is determined by our gut microbiome to a great extent, which needs raw vegetable fiber. He proposed to consider the gut microbiome as a separate organ of the human organism. He discovered membranous digestion and autolysis phenomena, and the mechanism of self-digestion of raw foods as well. The main idea of the autolysis phenomenon, he discovered, is that food digestion is determined by enzymes contained in a product, and gastric juice only induces the mechanism of food self-digestion. Ugolev believed that a human being is neither "herbivorous", nor "carnivorous", but "frugivorous", and fruits, nuts, fresh herbs, and root vegetables should form the basis of nutrition [68]. Following the above-mentioned ideas, it is interesting to recall the results of a broad-scale and well-funded Chinese study conducted over many years in 65 prefectures of the People's Republic of China (PRC) under the guidance of Colin Campbell (Cornell University, the USA) [60]. The object of his study became the correlation of statistical data of mortality from 48 types of cancer in 65 prefectures of PRC in the periods of 1973 to 1975 and 1983 to 1984, and preferences in nutrition and biochemical composition of blood samples of 6,500 residents. According to the authors, who analyzed about 8,000 correlations, there is evidence of a positive correlation between the consumption of animal origin foods from 1983 to 1984, and the rate of mortality from Western diseases (such as cancer and diabetes, being among the main factors of mortality) in 1973 to 1975, and negative correlation between consumption of plant-based food and statistics of mortality [60].

Although long-livers usually consume mixed food (of plant and animal origin), the benefit of garlic bulbs (*Allium sativum* L.) in the prevention of cardiovascular and oncologic diseases was recognized both in many cultures and proved by research [69, 70]. For a good reason, it constitutes the base of, for example, Jewish cuisine. Such products like reishi mushroom (Lingzhi), *Ganoderma lucidum* (Korea), and cordyceps, *Cordyceps sinensis* (China) should be mentioned among other products having universal therapeutic properties.

Lifestyle, namely, eustress mode and physical activity

It includes physical activity, cold training, sexual relationships, character, use of Eastern practices, Dao Yin Yang Sheng Gong, Qigong, Yoga, humor, and non-confrontation and acceptance of own age. Several authors recognize lifestyle as a determinant of active longevity [1, 5, 6, 12–16, 71, 72], including physical activity, cold training, engagement to spots and the Eastern practices (Qigong and Yoga systems), optimism, and a sense of humor. All these components of a healthy lifestyle neutralize the action of stressors and aftermaths of stress (general adaptive syndrome) negative for health, which are numerous in everyday life [73–76]. The main events of life happen against the background of stressors of different natures and forces. Everyone should adapt to them and be able to turn this stress into the eustress of daily life. The founder of the stress concept, Hans Selye, noted the dual nature of general adaptive syndrome that may lead to disease and destruction of the organism but also may increase the stability of the organism to unfavorable conditions [73, 74], introducing the concepts of eustress and distress for defining different kinds of reactions to stress. Distress is defined as a state when after the action of the stressor, adaptive possibilities of the organism are lessened, and if adaptive capacities increase, when it is eustress [75, 76]. Eustressors are characterized by not very powerful and brief impact. Morning exercises, cold training, physical activity (the rule of 10, 000 steps), love, watching theatre pieces, and an optimistic view of life are like that. In the paper [75, 76], it is pointed to the fact that the positive, formative role of stress is not highlighted in the literature. It is critical to move beyond the pathological model boundaries of stress following in the footsteps of Selye, who considered that there would be no life without stress [73, 74] and turned to positive conceptions and cognitive studies that may throw some light upon the mechanism of eustress [76]. The volume by psychologist McGonigal from Stanford University, the USA, was published in the form of an essay “good stress” [77]. There the author proposed changing attitude to stress and stated that good stress (eustress) [75, 76] is a way to become stronger and better, it gives energy, strengthens the heart muscle and enhances intuition [77]. Thus, the eustress regime is formulated as the integral factor of active longevity.

There are several approaches to explain the mechanism of the eustress phenomenon. In particular, the phenomenon of hormesis [78] can be considered as an eustress physiological mechanism, which represents a positive effect of small doses of strong stressor. Non-specific adaptive reactions of human organisms (NSAR) to external influences could be also considered as eustress mechanisms at the NSAR stages of “training” and “activation”, according to Garkavi et al. [79]. From the psychological point of view, the mechanism of eustress could be explained by the theory of posttraumatic growth for the cases when people begin to develop positively after experiencing a catastrophe [80].

Apart from the listed above, one of the basic components of this regimen is physical activity and sports, as well as Eastern practices, Qigong, and Yoga. A lot of literature and studies are devoted to the positive role of physical activity, physical training, and sports in forming health. However, a recently finished international epidemiological study of morbidity and physical activity ratio over 30 years proves that existing norms of physical activity (150 min a week) are lowered 5 to 6 times [81]. The effect of physical training on higher nervous function and genetic predisposition is studied. In particular, positive modification of genetic predisposition in physically trained people (athletes) is exemplified by genes controlling the system of hemostasis [72], and disposition to the disease of the 21st century, depression, to which not timely corrected chronic stress may lead [71].

“Muscular joy”, prominent musculature, and physical strength could not be considered as the only aim of exercises. Practices that strengthen the inner muscular system and ligaments, breathing, cognitive functions, improving blood stream and lymphatic drainage, and energy level of the human organism are a lot more important for health-forming, being aimed to longevity. This result is usually achieved by Eastern practices, Qigong and Yoga [5–7], not sufficiently studied from the point of view of evidence-based medicine. However, Yoga systems are thoroughly adjusted by physicians for the therapeutic correction of a wide range of diseases, from locomotor apparatus to cardiovascular system and neurologic diseases [82]. In one study, experimental results in decreasing the level of stress by Yoga asanas were provided, giving evidence of a statistically relevant decrease of the stress hormone, cortisol (and increase in testosterone) in the blood of Yoga athletes doing asana with flexion, Bhujangasana (cobra pose) with a stimulating influence on the area of kidneys, and therefore on adrenal glands [83].

As it is well-known, traditional Chinese medicine (TCM) originated in ancient China and is now a national heritage of the country, did not gain understanding from the part of the anatomy-based medical community earlier, as it operates incomprehensible terms of channels, meridians, and acupuncture points. Western medicine discovered Chinese medicine for the rest of the world when Chinese physicians demonstrated surgery without anesthesia to a delegation from the USA [5]. In 1998 in PRC, Chinese biophysics managed to show the fiber-optic nature of channels and acupuncture networks as well and illustrated that along them particular streams of low molecular substances and metabolites flew in the body, and energy redistribution being occurred [6]. It drew TCM to the standards of Western medicine (now TCM and Western medicine both demonstrate a scientific approach to health problems and represent current evidence-based medicine) and revealed a new way of application of TCM methods to form productive longevity. Nevertheless, it is a well-known fact how difficult it might be for a creative person to tune oneself to the mode of eustress, do morning gymnastics, practice Qigong positions and exercises or Yoga asanas, instead of working in front of two personal computers shortly after awakening to check an email box and finish writing a text started last night. Sometimes longevity determinants nutrition and lifestyle are combined in a common lifestyle factor with a big input to longevity phenomenon.

Heredity and genetic background

Genetic factor determines naturally the health and life duration of a person to the great extent. The heredity input to longevity phenomenon was considered up to 30% even a decade before. Naturally, if you have long-living ancestors in your family, then you have no bad chances to live longer. A genetically homogeneous population of long-livers exists in "Blue zones" [51–55] and in some non-validated mountainous or/and seacoast areas [56–58], and it was formed over centuries as a result of their long-living in these special geographic regions. Super long-livers are very rare events, e.g., recently, there appeared some doubts concerning the validation of French long-liver Jeanne Calment [84, 85]. Now it is possible to view the list of the validated world-oldest people (https://en.wikipedia.org/wiki/Oldest_people).

It seems that neither an aging gene nor a longevity gene exists since socially human important pathologies are not only multifactorial but also multigenic ones [2, 85]. According to one of the assumptions aging appears to be a disease, and it could be possible to find a way to knock the "aging gene" out [86, 87]. Nevertheless, there are a number of works related to the genetics of aging and longevity. It would be especially noted that there is an increasing number of available genomes of very old people [86–88]. Assuming that aging drives the acceleration in morbidity rates, the international team, based on theoretician biologists of Russian origin, built a risk model to predict the age at the end of healthspan depending on age, gender, and genetic background [89]. Using the sub-population of 300,447 British individuals as a discovery cohort, they identified 12 loci associated with healthspan at the whole-genome significance level. The authors found strong genetic correlations between healthspan and all-cause mortality, life-history, and lifestyle traits. They thereby conclude that the healthspan offers a promising new way to interrogate the genetics of human longevity [89]. More specifically, major histocompatibility complex, class II, DQ beta 1 (*HLA-DQB1*), lipoprotein(a) (*LPA*), and cyclin dependent kinase inhibitor 2B (*CDKN2B*) loci are identified in relation to healthspan, they being before associated with parental longevity. The notable absence in their study of the gene variants around the apolipoprotein E (*APOE*) locus known for the association with the early onset of Alzheimer's disease requires special consideration. The authors used for calculations the genome-wide association studies (GWAS) developed by Aulchenko and colleagues [89].

It was shown that genetic risk factors have a substantial impact on healthy life years [90]. The impact of genetic variation on overall disease burden has not been comprehensively evaluated. The authors introduce an approach to estimate the effect of genetic risk factors on disability-adjusted life years (DALYs; 'lost healthy life years') [90]. They use genetic information from 735,748 individuals and consider 80 diseases. Rare variants had the highest effect on DALYs at the individual level. Among common variants, rs3798220 (*LPA*) had the strongest individual-level effect, with 1.18 DALYs from carrying 1 *versus* 0 copies. Being in the top 10% *versus* the bottom 90% of a polygenic score for multisite chronic pain had an effect of 3.63 DALYs. Some common variants had a population-level effect comparable to modifiable risk factors such as high sodium intake and low physical activity. Attributable DALYs vary between males and females for some genetic exposures [90].

Genetic associations with healthy aging were recently discovered among Chinese adults [91]. The genetic basis of overall healthy aging, especially among the East-Asian population is understudied. The authors conducted a genome-wide association study among 1,618 Singapore Chinese elderly participants (65 years or older) ascertained to have aged healthily and compared their genome-wide genotypes to 6,221 participants who did not age healthily, after a 20-year follow-up. Two genetic variants were identified ($P_{Meta} < 2.59 \times 10^{-8}$) to be associated with healthy aging, including the low-density lipoprotein receptor-related protein 1B (*LRP1B*) locus previously associated with long-lived individuals without cognitive decline. The study sheds additional insights on the genetic basis of healthy aging [91]. It was found that multivariate genomic scan implicates novel loci and haem metabolism in human aging [92].

As it was mentioned earlier according to genetic studies, physical activity counteracts genetic susceptibility to hematological diseases [72] and to depression [71]. Some genetic studies in the longevity area are done using model animals, but it is quite improbable to get interesting and correct results concerning human longevity using non-human models, especially insects. Epigenetic studies exploring the influence of various factors on aging and longevity have proven to be much more interesting and fruitful [93–104].

Health care system

Timely health care and early diagnostics of pathologies including oncology are important for maintaining health and longevity for potential long-livers. It is also essential for the regions where long-livers reside, though they become ill significantly rare, and die more often from infectious diseases. Two cases can be cited when the state and the government adopted special programs to improve the health of the population in their country. The first example is Japan, where a special state program began to operate for the rehabilitation of the entire population of the country after the 1945 atomic bombardments [55, 105]. Over a span of 50 years, this program led to an increase in the country's life expectancy, rising from 63 years to 82 years. This achievement was further facilitated by the widespread use of iodine-enriched laminaria products and gratis injections of medicine based on human placenta hydrolyzate known as "Laennec" (https://placentacare.com/home_eng) [55, 105]. The second well-known case of the state healthy lifestyle program is Finland, where mortality from cardiovascular diseases has dramatically reduced due to the action of the special state program "North Karelia" [106, 107]. Finnish men in the North Karelia region had the highest mortality from heart disease in Europe and even in the world at that time due to cardiovascular disease risk factors: increased serum cholesterol, elevated blood pressure, and smoking. In response to a local petition to decrease deaths from heart attacks, the North Karelia Project was launched in 1972 to serve as a population-based intervention focused on public health risk factor reduction and prevention of cardiovascular diseases through lifestyle changes including a dramatic decrease in dietary fat eating, increased consumption of fruits and vegetables, outdoor physical training, prolong walks, and stop smoking [107].

Mental state, meditation, and state of mind

State of mind and meditation are generally known for their use in forming health through Qigong and Yoga systems and some other medical practices [5–8]. An important epidemiologic study of recent years on the influence of religious worship (prayers during visits to religious institutions) on the decrease of mortality risk from cardiovascular or oncologic diseases calls attention to itself [108]. The authors of this latest study published in the peer-reviewed journal the Journal of the American Medical Association (JAMA) analyzed 74,000 medical histories in 20 years, suggesting that this aspect represented a currently unused source of health improvement for the population and patients. Cases, when oncologic patients were cured after a prayer in church, are described. Children's plays and prayers of adults are nothing else but meditations that are broadly used in traditional national practices. This is the first epidemiologic study of the therapeutic potency of prayer and its role in the prevention of socially important diseases of such a scale, done from the standpoint of evidence-based medicine. The role of meditation in forming health was emphasized not only in traditional systems of Qigong and Yoga [5–8] but also by the modern researcher of active longevity, Amosov [13]. Such a transdisciplinary approach to forming health is often demonstrated by representatives of creative intellectuals, culture, and business using all the achievements of civilization, including evidence-based medicine, and practicing Qigong or Yoga systems, and their number is growing.

Motivation to live longer

Besides the above-mentioned factors, people should have the motivation to live long; one should have compelling reasons, why he or she needs it. As well in the case of health, marked motivation significantly increases the chances for productive longevity.

Conclusions

1) Long-living is endemic and emerges in coastal (Blue zones) or mountain areas (approximately 500 to 1,800 meters above sea level) with unique climates, the composition of water, and the atmosphere. Long-livers typically have low-calorie nutrition (approximately 800 to 1,200 kcal), their nutrition being rich in vegetables, nuts, and fruits, often unique ones; legumes (lentils, beans, corn, soybeans) hold a special place in their nutrition. They are enormously active physically and socially, use other DPL, and their life is full of sense (according to "Ikigai" in Japan).

2) Health is the ability of human organism conducing to physical, mental, and emotional strain and relaxation after it.

3) Genetic factors and special characteristics of nutrition have a decisive contribution to the phenomenon of longevity. Only a few genes are proven as linked with longevity.

4) Nutrition is one of the crucial inputs to the creation of natural longevity phenomenon. Vegetarianism and consumption of plant-based food (fiber), fruits, and vegetables (5 successions in a day) decrease the risk of diseases (oncologic and cardiovascular ones) and increase lifespan. Long-livers use garlic, chili pepper, reishi mushrooms, and cordyceps.

5) Eustress ("good" stress) also appears to be a decisive determinant of active longevity, namely physical activity, cold training, sexual relationships, sports activities, Eastern practices (Qigong, Yoga), and optimism. Physical activity modifies genetic predisposition to diseases of the hemostatic system and depression. Asanas of Yoga as well as Qigong movements represent mild stressors and improve the endocrine profile and balance of energy.

6) Each of the other determinants, such as health care, motivation, and meditation (state of mind), prayers, and meditations may substantially contribute to the creation longevity phenomenon.

Abbreviations

Cd: cadmium

DALYs: disability-adjusted life years

DPL: determinants of productive longevity

PRC: People's Republic of China

TCM: traditional Chinese medicine

vWF: von Willebrand factor

Declarations

Author contributions

RIZ: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Supervision. RNK: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. RIK: Validation, Writing—review & editing, Supervision. AE: Investigation, Writing—original draft. ASS: Conceptualization, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

The work was funded with the regular state support allocated to Kazan State Medical University and Interregional Clinical Diagnostic Center, Ministry of Health of the Republic of Tatarstan, Kazan, Russia. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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