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Beyond calories: an integrated approach to promote health, longevity and well-being

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Abstract

In 1948, the World Health Organization defined health as “a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity”. Detractors claim that this definition of health is utopian and unrealistic. However, accumulating evidence from experimental studies suggest that aging is not inevitably linked with the development of chronic diseases, and age-associated accumulation of molecular damage can be prevented or greatly delayed by dietary and genetic manipulations that down-regulate key cellular nutrient-sensing pathways. Nonetheless, to obtain a state of complete physical, mental, and social well-being, we as human beings need to go beyond nutrition or pharmacological treatments, and implement a combination of interventions that enhance not only our metabolic health, but also our psychological, emotional, intellectual and spiritual development, our social relationships and cultural well-being. This perspective highlights a range of scientific research-based interventions that can potentially be used to promote human health and longevity. We will also briefly address the importance of environmental health in achieving this goal.

Keywords

Healthy Aging; Quality of life; Nutrition; Diet; Exercise; Environment; Longevity

Introduction

According to the World Health Organization, health can be defined as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Detractors claim that this definition of health is utopian and unrealistic. However, accumulating evidence from experimental studies indicate that aging is not inexorably associated with the development of chronic illnesses, and the age-associated accumulation of molecular damage can be prevented or greatly delayed by dietary and genetic manipulations that down-regulate key cellular nutrient-sensing pathways [1]. Nevertheless, key questions

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remain: will calorie restriction, intermittent fasting or any other dietary or pharmacological intervention alone help us to attain such a state? Or do we need a wider perspective and an integration of multiple strategies to achieve this goal? What are these interventions? When they should be initiated? What are the biological mechanisms through which such interventions operate? Beyond the physical well-being of the individual, how important are the psychological, emotional, intellectual, and spiritual development, and the social relationships and cultural well-being of the whole community in promoting health and well-being? And finally, how important is the health of the environment in which we live and work in influencing our metabolic, psychological and social health? We believe that these are some of the key questions that the scientific community needs to address in order to design and build a better world, in which human beings can flourish, enjoy a long healthy life, and fully realize their potentials, without damaging the planet. In this viewpoint article, we will summarize a range of scientific-based interventions that can be used to promote human health and longevity. We will also briefly address the importance of environmental health in achieving this goal.

Nutrition and health

Accumulating data strongly indicate that nutrition is the most important intervention for the promotion of health and the prevention of the great majority of age-associated chronic diseases. Hundreds of pre-clinical studies have shown that calorie restriction without malnutrition, by inhibiting key nutrient-sensing pathways [1], powerfully slows aging, and prevents or delays the onset of many degenerative chronic diseases, such as cancer, cardiomyopathy, nephropathy, neurodegeneration and many autoimmune diseases in model organisms. More recent data show that calorie restriction without malnutrition drastically reduce cancer and cardiovascular morbidity and mortality, prevents diabetes, and attenuates age-associated neurodegeneration, sarcopenia and auditory loss in non-human primates [2-4]. In humans data from observational studies and clinical trials show a CR-mediated significant improvement in metabolic and molecular health as well [4-6]. However, it is not known yet which is the ideal calorie intake associated with optimal activation of cellular pathways that prevent or delay the accumulation of molecular damage leading to multiple age-associated diseases. For example, experiments in several recombinant inbred mouse strains show that the response to 40% CR exhibits wide variation, with some strains living longer and other shorter than the ad-libitum fed controls [7]. Preliminary data suggest that strains with shortened lifespan under 40% CR may live longer under less stringent CR, depending on sex and age when CR is started [8]. Most likely, the same applies to humans. A certain degree of CR that is ideal for some men or women, might be excessive and cause damage in others. Moreover, accumulating data suggest that meal timing and the quality of diet both play key roles in promoting health and longevity, independently of calorie intake. As reviewed elsewhere, intermittent fasting, adjusted diurnal rhythm of feeding, and restriction of protein or specific amino acids in the diet seem to promote an increase in healthspan and/or lifespan in multiple model organisms, even in the absence of changes in overall calorie intake [9]. Clinical studies are underway to determine the metabolic and molecular effects of these and other dietary interventions in humans. Nutritional modulation of gut microbiome structure and function, especially early in life, may also play a crucial role in promoting metabolic health, in preventing diseases, and in shaping the neurological

development and immune function [9-11]. For example, it has been shown that short-chain fatty acids derived by the fermentation of indigestible fibers shape the immune system and inhibit inflammation, whereas trimethylamine-N-oxide derived by gut microbiota metabolization of certain meat-derived compounds increases cardiovascular disease risk [9-11]. Overconsumption or deficiency of other nutrients or chemicals, such as trans-fatty acids, saturated fatty acids, nitrosamines, polycyclic aromatic hydrocarbons, polyunsaturated omega-3 fatty acids, vitamins (e.g. vitamin C, E, B complex, folic acid, beta-carotene), phytochemicals (e.g. polyphenols, terpenes, sterols, indoles, and isothiocyanates), minerals (e.g. sodium, potassium, iron, iodine) and oligo-elements (e.g. selenium, magnesium, manganese) have additional detrimental or beneficial effects on individual metabolic processes that can lead to specific diseases [11].

Physical exercise and health

Much like the air we breathe and the food we eat, movement is essential for our physical health. This is because over thousands of years, we have evolved to engage in enormous amount of physical activity. Our body is metabolically and genetically programmed to operate at its best only when supplied with constant, regular, but not excessive, physical activity. Not surprisingly, several epidemiological studies have shown that physically active individuals are healthier and live longer than sedentary ones [12]. Moreover, sedentary people have a greater risk of both mortality and disability. A recent study suggests that prolonged periods of inactivity (for example the number of hours per day spent in a sitting position watching television or working at a computer) are associated with an increased risk of developing and dying from cardiovascular disease, cancer and diabetes mellitus, regardless of the number of exercise sessions per week [13].

Although traditionally the emphasis has often been on the importance of aerobic exercise involving the activity of the large leg muscles, the scientific research data suggest that a complementary program of anaerobic and flexibility exercises induce additional positive effects on muscle strength, resistance to stress, metabolism, cardiac function, coordination, balance, flexibility and psychological well-being. As reviewed elsewhere, endurance or aerobic exercise is more effective in (1) increasing mitochondrial biogenesis and the consumption of oxygen and calories, (2) improving cardiopulmonary function, (3) insulin sensitivity and (4) reducing cardiometabolic risk factors [14,15]. The benefits of aerobic exercise are not confined to the cardiovascular system. It has been shown that aerobic exercise, by reducing the circulating levels of insulin and estrogen, decreases the risk of developing some of the most common cancers, such as breast cancer, colon cancer and endometrial cancer [16]. A recent study conducted in Australia showed that 6 months of an exercise program of moderate intensity (walking 50 minutes three times a week) would be able to significantly improve the plasticity of the brain and cognitive function in patients with mild cognitive impairment [17]. Preclinical and clinical studies suggest that these benefits may be partly due to the production of brain derived neurotrophic factor (BDNF), the stimulation of cerebral perfusion and angiogenesis, and an improvement in the integrity of the neurovascular and synaptogenesis [18]. Anaerobic or isometric exercise, however, is more powerful than endurance exercise in: (1) increasing skeletal muscle mass, strength and power, (2) preventing sarcopenia, osteoporosis and falls (which are the causes of bone

fractures of the elderly), and (3) promoting functional independence [19]. In addition, the increase in muscle mass caused by physical anaerobic exercise helps to raise the basal metabolic rate, adding to the benefits of aerobic activity [19].

Health and cognitive training

The brain is a dynamic and plastic organ that has the ability to constantly learn new skills, integrate new experiences, and form and retain long-term memories. It has been shown that stimulation of the mind improves brain function and protects the brain from cognitive decline, just as physical exercise helps prevent the loss of bone and muscle mass. The human brain is able to adapt to external conditions and reprogram itself continuously. The external and internal stimuli of human experience induce a rearrangement of the architecture of the brain and synaptic connectivity of the cerebral cortex [20]. However, this brain plasticity, which peaks in children and adolescents, is reduced with age, especially in the absence of adequate stimulation and exercises that enhance mental abilities [21,22].

It has been shown that mice exposed to stimulating environments rapidly increase the turnover of synapses, while exposure to low-stimulation environments inhibits this activity [23]. In the adult, even modest modifications of synaptic connections, such as the formation of new dendritic protrusions induced by new experiences, correlates with improved ability to learn and to memorize motor, sensory and contextual tasks. It has also been demonstrated that daily learning and sensory experiences leave small but permanent traces on cortical connections, and that long-term memories are stored in stable networks of synaptic connections [24].

Although in adults the ability to form new dendritic synapses in response to sensory stimuli is lower than in children, it has been shown that a cognitive training program with different mental exercises (e.g. crossword and jigsaw puzzles, sudoku, computer games), which activates one or more cognitive domains, is clinically effective in improving cognitive function, probably through a strengthening of the synaptic circuits [25]. Studies with electroencephalography and functional magnetic resonance imaging have demonstrated that electrical activity and metabolism of specific brain areas are changed in response to these cognitive exercises, and that these changes are maintained for a long period even after the end of training. Rac1 and NMDA receptors, for example, seem to be involved in the process of hippocampal neurogenesis induced by learning [26].

Clinical studies suggest that cognitive stimulation programs designed to improve memory can activate multiple brain areas also in patients who are already suffering from initial cognitive deficits, suggesting that the healthy areas of the brain are able to compensate for the lack of activity of the damaged areas [27]. In a randomized trial involving 2,832 older people, 10 sessions of exercises to develop verbal episodic memory, inductive reasoning, and speed of data processing (visual search and identification) induced a significant reduction in functional decline and improved cognition, effects that persisted for 5 years after the start of the intervention [28].

Accumulating data suggest that it is key to stimulate the brain by learning new tasks, especially complex tasks that require the involvement of multiple functions (e.g. motor and

sensory) and brain areas, such as learning to play a musical instrument or a new language, or starting new activities such as dancing, yoga, or chess [29]. It has been shown that painting and sculpture helps to develop agility and hand-brain coordination, as it stimulates brain plasticity [30]. Another potential and simple technique to trigger the formation of new neuronal circuits is performing the movements with the non-dominant hand. For example, eating food or handling the mouse with the non-dominant hand forces the brain to re-learn some common tasks in a new way.

Sleeping and cognitive health

Sleep plays also a strategic role in promoting health and well-being, and in consolidating long-term memories. During deep sleep (slow wave sleep or stage 3 and 4), neurons and neuronal networks, that had been activated during the day in response to the various experiences, are reactivated in multiple brain regions. The expression of numerous proteins needed for synaptic plasticity increase during the first few hours of sleep. A recent study suggests that sleep improves memory consolidation in the long term, decreasing dopaminergic activity [31]. On the contrary, neuronal activation during wakefulness increases dopaminergic activity and accelerates the oblivion of information recently acquired [32].

Some recent preclinical studies suggest that alterations of sleep, and sleep fragmentation in particular, play a role in the pathogenesis of Alzheimer's disease and are an early sign of cognitive impairment [33]. Sleep deprivation increases Aβ plaque formation and induces neurodegeneration, while improving the quality of sleep reduces the accumulation of plaques. Moreover, in a vicious cycle, the deposition of plaques worsens sleep quality, decreasing the amount of deep sleep, which correlates with a deficit of memory consolidation [33].

It has been shown that both cognitive exercises that stimulate the formation of new synapses (e.g. exercises for the memory development) and physical activity increase the duration of deep sleep [34]. Recent preclinical studies suggest that sleep stimulates the activation of mechanisms (glialymphatic pathway) that cleanses brain cells of toxic proteins [35], improves immune function [36] and activates the parasympathetic system [37], which has anti-inflammatory effects.

Meditation and health

Another method that can be employed to improve cognitive abilities and psychological health is mindfulness meditation. Some studies have shown that a meditation program is able not only to improve the quality of sleep, but also to increase the plasticity of some areas of the brain, strengthening the ability to process and store data [38,39]. Meditation techniques associated with reduced respiratory rate are able to inhibit the activity of the sympathetic system while activating the parasympathetic system [40]. Interestingly, it has been shown that the stimulation of the parasympathetic or vagal system inhibits inflammation. In fact, acetylcholine, released from the vagus nerve endings represses gene expression and the secretion of inflammatory proteins by binding to specific inhibitory receptors on macrophages [41].

Other studies have shown that meditation may also be helpful in reducing psychological stress. The acquisition of introspection skills via meditation is associated with lower levels of neuroticism, anxiety, and depression, as well as higher levels of self-esteem and satisfaction [42]. One trial conducted in 40 young students showed that practicing meditation for 20 minutes each day for five days significantly increased attention, and reduced conflict, anxiety, symptoms of depression, fatigue, and cortisol levels [43]. Moreover, people who meditate on a regular basis tend to acquire, over time, a greater capacity for introspection, self-awareness, self-control, and management of emotions, which reflect the optimal integration of autonomic, affective and cognitive processes. Meditation teaches us to observe and more fully enjoy the experiences that life offers, enhancing our emotional and intuitive intelligence.

Social relationships and health

The results of several epidemiological studies suggest that social relationships are key determinant of health and longevity [44]. Socially isolated people are psychologically and physically less healthy, and have a higher mortality. For example, mortality in unmarried people is higher than in married ones; moreover, the risk of death doubles in men and triples in women within the first month after the spouse's death [45]. Other epidemiological studies have shown that psychological well-being is associated with improved immune function and reduced inflammation [46].

Some of the negative effects associated with social loneliness are due to psychological stress, which is a known risk factor for myocardial infarction and stroke. Psychological stress, for example, induces the activation of the catecholaminergic system, which is reflected in increased blood pressure, heart rate, and immune system activation [45,46]. Epidemiological studies suggest that socially connected, serene, cheerful, optimistic, happy, confident and satisfied people are healthier and live longer than those who feel stressed, depressed, isolated and wrathful [44]. The results of a meta-analysis of 24 studies suggest that happy people live longer than persons who reported that they are unhappy [47]. Happier people are also less likely to commit suicide, and they are less often the victims of accidents.

Environment and health

The quality of the environment in which we live, work and perform most of our daily activities, both indoor as outdoor, deeply influences our health. The quality of the air we breathe, of the water we drink, and of the ground in which we grow our food have important repercussions on our health. Beside the well-known detrimental effects of smoking, accumulating data indicate that air pollution, in particular fine particulates (PM2.5), is positively associated with an increased mortality from cancer and cardiopulmonary disease [48]. Major contributors to air pollution are: (1) burning of fossil fuels to produce energy for heating/cooling of buildings, transportation, industrial activities and manufacturing, (2) waste incinerators and refineries, and (3) industrial agriculture and farming. Moreover, combustion of fossil fuels and intensive agriculture and animal farming contribute to approximately 80 and 20%, respectively, of worldwide annual greenhouse gas emissions leading to global warming and its potential harmful consequences, including drought and land desertification, floods due to more frequent and devastating storms, and diffusion of

climate-sensitive infectious diseases [49]. Water and soil pollution, caused by excessive use of chemical fertilizers, pesticides, and antibiotics in intensive agriculture, inefficient disposal of industrial waste, the mining of toxic metals, and nuclear accidents, are also responsible for increased morbidity and mortality in humans, and for serious environmental issues, including acid rain and eutrophication resulting in toxic algal blooms, increased incidences of fish kills, and loss of biodiversity [50]. Significantly reducing environmental pollution is possible, but requires a profound revolution in the way we think and conduct our lives. As reviewed elsewhere, we need to design a new environment-centered industrial and economic system that favors energy efficiency and promotes integrated modifications in the use of the world's natural resources, with the objective of achieving a wiser use of energy, better farming systems, and healthier dietary habits which favor minimally-processed plant-sourced foods over animal-derived food products [50].

CONCLUSION

Although, it is known that the genes we inherit from our parents play a role in the risk of developing certain diseases and dying prematurely, it would seem that the environmental factors are far more important. Longitudinal studies of identical twins suggest that no more than 20 to 30% of the variance in longevity is explained by the inherited genes; the same applies to most tumors [51], which implies that our environment and lifestyle are crucial to our health and well-being.

We must remember that the aging process, and the accumulation of molecular damage over time which leads to functional and structural decay of the body, begins in utero and not when we turn 65 [9,52]. Therefore, achieving a healthy and balanced lifestyle from an early age is vital, and we need to stick to it if we want to minimize the risk of getting sick and if we aspire to live a long, healthy, and happy life. For example, despite a similar 30% reduction in serum LDL-cholesterol, the reduction in coronary heart disease events in individuals with PCSK9 mutations is much greater (nearly 90%) than in individuals taking cholesterol lowering medications (approximately 30%), most likely because the former have low serum LDL cholesterol levels all over their entire life, and they may never have developed atherosclerotic plaques. In contrast, high-risk patients enrolled in the statin trials had already developed atherosclerotic plaques, which probably necessitate much more severe LDL lowering to prevent an event [53].

As previously discussed, the preclinical and clinical studies conducted so far show that dietary restriction with adequate intake of specific nutrients, in conjunction with physical and cognitive exercises are powerful tools to prevent or slow down the accrual of cellular damage, leading to cell dysfunction and tissue degeneration. Accumulating data from animal studies suggest that in the near future specific pharmacological treatments, which target key pro-ageing pathways (i.e. IGF-1-mTOR, HSF-1), could be combined with personalized lifestyle interventions to potentiate their protective effects [52]. However, to assure our future health, it is also necessary to plan and implement policies now that improve human and environmental health literacy; enhance the livability of our towns and the energy efficiency and resilience of our buildings and vehicles; increase non-motorized transport,

urban green spaces and parks; improve the farming systems and an adequate use of natural resources, so that we can preserve our “Natural Capital”.

In conclusion, we believe, unlike the WHO health definition detractors, that a basic life aspiration of every human being should be to achieve a complete state of well-being, surmounting the suffering inflicted by physical, mental, and spiritual illnesses. We think that to obtain a real and lasting state of health and well-being it is essential to live in a healthy environment, eat a nourishing diet that activates anti-aging molecular pathways, and to practice a range of physical and cognitive exercises that enhance our physical strength and resilience, and our emotional, intuitive and creative intelligence. Only then will we be able to lead a fulfilling life into old age and to share the wonderful experiences that life can offer us with our family and friends.

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