Potential Factors Affecting Human Longevity

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Abstract: Longevity has been a topic of fantasies throughout the entire human history and fantasized by people on all spectrums. The concept of life has attracted many towards it. Numerous studies have been done on longevity, but none have a definitive answer on how to achieve longevity, with results ranging wildly from Calorie Restrictions to genetic expression. Environmental aspects such as smoking and PM2.5 also seem to contribute to the case. The current consensus on longevity is that there is no definitive answer to it as recent advancements in the field highlight multiple factors in play, deteriorating or repairing the human body. This review will cover some environmental, behavioral, and genetic aspects of longevity.

1. Introduction

The term longevity has been mentioned and studied from ancient times to the present day, and in recent years scientists have made certain developments to slow down the aging process. The term longevity has been mentioned and studied from ancient times to the present day, and in recent years scientists have made certain developments to slow down the aging process. The research on NAD+ is dedicated to the activation of sirtuin to inhibit MTOR, and to the modification of diet, work and exercise to achieve the effect of slowing down the aging process. There is a wide range of research aspects of longevity and the factors that contribute to longevity vary. Therefore, the main study in this thesis is to show the relationship with longevity from different factors. We will begin to introduce the mechanism and function of the gene, sirt1. How genes determine lifespan and influence offspring and activation of sirt1 by NAD+ to maintain cellular health against ageing. Finally, we will cover the effects of food intake, vitamins and the environment we live. Training on health, cardiovascular and cerebrovascular.

2. Genetics

Genetics play a large role in longevity. A survey of 477 Ashkenazi Jewish individuals of age 95 years or older shows that the maximum body mass index of these exceptional long-livers is similar to the body mass index of 1838 average white males and females collected from the National Health and Nutrition Examination Survey [1]. Many of the 477 also report smoking and alcohol consumption at a younger age as well. Another study from the Long Life Family Study (LLFS) suggests that offspring of long living families tend to have significantly lowered chances of age-related diseases such as Alzheimer's, diabetes, heart failure, chronic kidney disease, and more [2, 3]. In these examples, the people investigated did not conduct especially healthy lifestyles, yet they still gained a healthier and longer lifespan, meaning that more is at play.

2.1 SIRT1

SIRT, short for Silent Information Regulator 2 (Two), is one of the genes associated with longevity [4]. There are seven variants of this gene, coding for various NAD+ dependent de-acetylases named

Sirtuins. These NAD+ dependent de-acylases typically deacetylated lysine residue on substrates and along with breaking down NAD+ to nicotinamide and 2'-O-acyl-ADP-ribose [5-7]. Of the seven Sirtuins, we will be covering the SIRT1 gene and Sirtuin 1 in this part.

2.2 Enzyme Structure

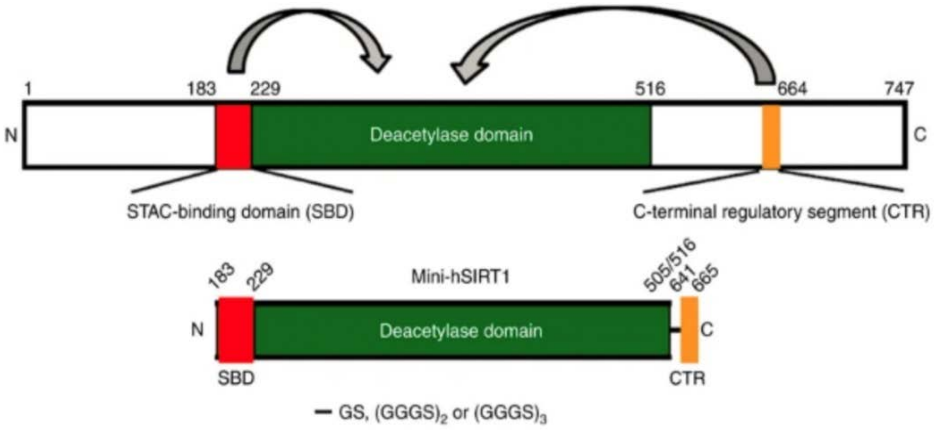


Figure 1. Model of basic Sirtuin Structure [8]

Crystallography of Sirtuin 1 identifies three main regions of the enzyme, the central domain with basic catalyst structures for deacetylation, the N-terminal SBD that mediates binding, and C-terminal CTR peptide which stabilizes the central domain [5].

2.3 Function

Sirtuin 1 localizes itself in the nucleus, expressed in brain, heart, kidneys, liver, and most of the human body parts. This single enzyme coded by the SIRT1 gene is responsible for mediating many different aspects of cell health induced by energy control [4, 5, 8]. When activated as a NAD+ particle binds with the Sirtuin 1 enzyme, the central domain latches onto an acetyl group on a histone protein and catalyzes a reaction between the acetyl group and NAD+ to yield nicotinamide and 2'-O-acyl-ADP-ribose, electrically attracting the DNA strands tighter to the histone proteins, making it harder to transcribe. Sirtuin 1 also works on non-histone proteins. In this case, it acts as a transcription factor, deacetylating the protein to increase its efficiency [9-12].

2.4 Sirtuins in Apoptosis

One such areas that Sirtuin 1 regulates is apoptosis, programed cell death. Apoptosis normally happens when a cell cumulates so much damage that it could no longer function as a healthy cell to the body [12]. However, apoptosis can happen too early, leading to neural degeneration, various heart diseases, and osteoarthritis [12]. Sirtuin 1 deacylated some of the proteins such as p53 and forkhead family proteins, deactivating said proteins, making it less likely for apoptosis to occur [13, 14]. For example, Koji Takayama et al conducted an experiment on six human kneecap cartilages, observing the effect of Sirtuin 1 on chondrocytes by inhibiting and activating Sirtuin 1 using nicotinamide and resveratrol respectively. The results, as expected, were that the cartilage with inhibited Sirtuin 1 was damaged harder than the cartilage with activated Sirtuin 1. It is observed that more of the chondrocytes trying to repair the cartilage under cellular stress underwent apoptosis when Sirtuin 1 got suppressed.

This decrease of apoptosis under cellular pressure means that cells protected by Sirtuin 1 can live longer and duplicate more, filling in the constant cell loss of an organism, therefore increasing lifespan [13].

2.5 Sirtuins in Inflammation

Another area is inflammation; It is usually a mechanism the human body uses to defend against infections, injuries, and toxins [10]. Inflammation triggers as a response to trauma in order to scour for microbial infections [15]. Though, like apoptosis, inflammation is not a perfect process. There are two

types of inflammation, acute and chronic. Several serious diseases could be caused by over inflammation, many of which could and will result in early death, shortening one's lifespan [15, 16]. As acute inflammation occurs due to any stimuli, pro-inflammatory and anti-inflammatory genes both switch on where the pro-inflammatory genes get suppressed shortly after activation [6, 10]. Chronic inflammation happens when acute inflammation fails to eliminate the threat at the stimuli, thus the immune system must activate for longer [16].

Sirtuin 1 performs the deacylation of anti-inflammatory genes from histones to recruit Re1B, a crucial element in repression of NFκB pro-inflammatory transcription pathways [11].

2.6 Epigenetic Regulatory Functions

The most important aspect of longevity Sirtuin 1 regulates would be epigenetic information maintenance [17]. A theory that aging is a demonstration of epigenetic damage is growing in prominence. As the human body grows older, DNA damage cumulates from various sources such as oxidation, ionizing radiation, and more. These DNA breaks usually gets fixed rather easily by the cell's repair pathways. But the epigenetics dictating gene expression of a specific gene may not be repaired [18]. Sirtuin 1 relieves this issue by two methods. First, being responsible of the deacetylation of other important proteins such as PGC-1α, Foxo4, p65, etc, which would in turn moderate the amount of cellular stress and prepare accordingly. Second, Sirtuin 1 also prevents abnormal methylation of our genes, maintaining genetic stability [18].

3. Air Quality (Pm2.5)

Recently, with the development of cities and the progress of industry, air pollution is becoming more and more serious. Normal gaseous pollutants and particles matter (PM) is included in air pollutants. It was found that PMs with aerodynamic diameter less than 10 μm and have a greater impact on human health.PM2.5 is known as a level 1 carcinogen with Harmful gases, heavy metals and other dissolved in the blood. It is very harmful to the body. The size of PM2.5 is equal to the twenty-eighth the diameter of a human hair. Since nasal hair can only block particles between PM75 and 100 when we inhale PM2.5 through our nose, even the cilia of mucosal cells can only block PM50. PM2.5 then reaches the throat, but it is so small that it goes into the bronchi easily and into the alveoli. And then it goes through the epidermis of capillaries, and then into the whole circulatory system. [19] There are immune cells called macrophages in the blood, and when PM2.5 enters the bloodstream, the macrophages eat it as a bacterium. However, PM2.5 is an inorganic substance that cannot be digested, leading to a buildup of particles that eventually overwhelm the macrophages. It will cause many diseases, such as bronchitis, asthma and so on.

4. Food Intake

The quantity of nutrition taken in impacts lifespan dramatically. Intuitively, the entity with healthier diet, would experience a longer lifespan due to less sickness caused by diet, better body composition, and more.

4.1 Caloric Restriction

Regarded as perhaps the most robust method of extending lifespan and healthspan of an organism, caloric restriction (CR) experiments where the organism tested is only given a sufficient supply of food to prevent malnutrition are consistently yielding positive results on the improvement to lifespan. The prominent theory that explains the life extending results is the disposable soma theory, a theory stating organisms will conserve their energy for self-preservation when nutrients are scarce and use energy for reproduction when nutrients are abundant [6, 20]. Experiments have been run on yeast, fruit flies, mice, fish, and they seem to be consistent with the theory [20], showcasing a reduced reproduction rate while living longer lives.

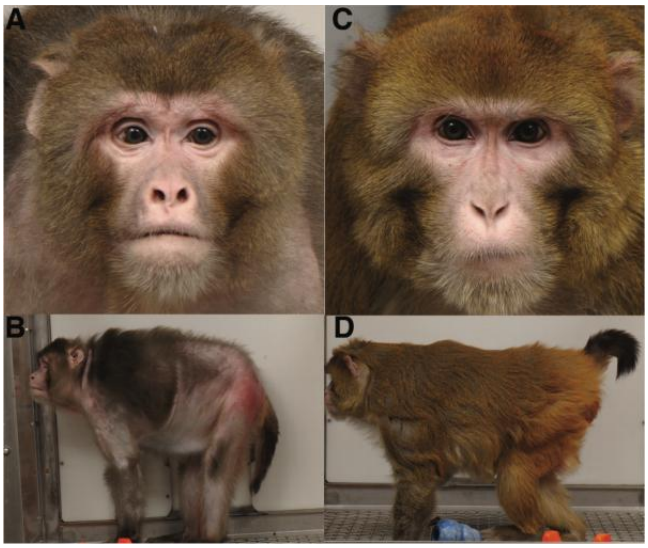


Figure 2. Comparison of monkeys with and without CR. CR monkeys on the right, control group monkeys on the left.

A 20-year study at the Wisconsin National Primate Research Center (WNPRC) on the effects of CR on rhesus macaques consisting of 76 7 to 14 years old monkeys shows that only 20% of the group of monkeys undertaking moderate calorie restriction died instead of the 50% mortality rate of the fed monkeys at the time reported, with 37% of the deaths of the fed monkeys due to age-related issues. These CR monkeys not just lived longer, but healthier too, their total body fat mass decreases, age related muscle mass decline (sarcopenia) is repressed, metabolic functions also improved, specifically insulin sensitivity to maintain glucose homeostasis, and more. Recent discoveries of the Sirtuin family of NAD+ dependent de-acylases, a family of enzymes that are responsible for regulating multiple cellular repair mechanisms, further support this claim [21].

Yet, another experiment by the NIA with monkeys of varying ages challenges the theory. Rhesus monkeys are again used and undergone CR, but no significant increase in lifespan is observed compared to the control group, though the CR monkeys did demonstrate improved metabolic profiles [22].

These studies on the rhesus monkeys remind us just how little we know about the specific mechanisms of CR. There are many caveats in CR to be explored as well. CR is observed to be less effective the later in life it is adopted by the organism. While a young mice could experience up to a 50% lifespan increase, an older mice may only experience 17% or less [6]. Though, these late life CR sessions still were found useful for some mice, with heart and kidney functions benefitting the most [6]. For example, mice of age 20 months endured 2 months of CR. Afterwards, the mice were observed to have cardiac functions like young mice, with bonus of decreased myocardial fibrosis and apoptosis.

To complicate the matters more, effects of CR vary depending on the genotype of mice. Goodrick et al. gathered mice with the A/J, C57BL/6J, and B6AF1/J strands of genes, and gave all the mice an Every-Other-Day (EOD) diet CR session. He found that while all mice gained the benefits of CR when CR is initiated at 1-2 months of age, but only in B6 and the hybrid mice when CR is initiated at 6 months of age [6].

Yet, the ultimate question still looms above all. Is the CR technique translatable to humans? Short term studies of CR in volunteers show benefits such as altered insulin signaling, reduced hormesis, and more [23]. A study on the Okinawans, a group of peoples living on the Japanese island of Okinawa, known for their longevity, displays that the all-cause mortality rate of 60–64-year-old Okinawans is almost half the average Japanese 60-64-year-old mortality rate. It is then found that the Okinawans get accustomed to a low-calorie intake diet at a young age. Okinawan school children only consumed 62% of calories of average Japanese school children, and adults report consuming approximately 17% less calories than the average Japanese, perhaps making them the living embodiment of CR in humans [24]. However, it might feel tempting to rush an answer considering the robustness of CR, but nuances

of the technique keep CR from widespread usage. The Okinawans are only one ethnical group and cannot represent the entire world. Differences in genotype may prove to be crucial or detrimental for long term CR in human beings. There are also concerns about the potential hazards of borderline malnutrition calorie intake for the human body, specifically the brain [19]. For now, CR should just be a method to investigate what its powerful effect on longevity implies.

4.2 Vitamin and Anti-aging

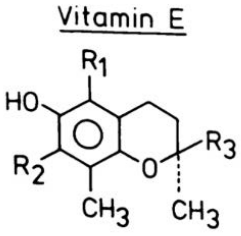
Vitamins are nutrients which human bodies need to survive but cannot synthesis. The tales of the horrible scurvy being treated by eating citrus, which is filled with vitamins, highlights the importance of vitamins.

Recent studies have also shown that vitamins may also have unique effects on battling aging.

Oxidative stress is a lifelong issue for any aerobic organism. Highly reactive chemicals called "Reactive Oxygen Species" (ROS) could form from oxygen in our respiratory system, and many other reactive particles with an impaired valence shell called "Free Radicals" could also be present as well [25, 26]. These free radicals can react to various structures in the body, not limited to lipids, proteins, and even DNA, potentially triggering adverse effects if unchecked, building up in the body, and playing a large role in the aging process [25, 26].

Fortunately, all vitamins protect the body from free radicals and ROS to varying degrees.

Vitamin E:



	R_1	R_2	R_3
α-Tocopherol	CH_3	CH_3	$C_{16}H_{33}$
β-Tocopherol	CH_3	H	$C_{16}H_{33}$
γ-Tocopherol	H	CH_3	$C_{16}H_{33}$
δ-Tocopherol	H	H	$C_{16}H_{33}$

Figure 3. Model of the structure of the general Vitamin E [27]

Vitamin E is a group of eight lipid soluble substances with a chromanol ring. There are two main groups of vitamin E, each with an alpha, beta, gamma, and delta variant. The ones with a saturated carbon side chain are called tocopherols, while the ones with an unsaturated carbon side chain are called tocotrienols [27-29].

Vitamin E is known for its antioxidative properties, especially the protection of cell membranes from lipid peroxidation. Vitamin E attains its anti-oxidative properties as a strong free radical scavenger of peroxide ROS thanks to its special chromanol ring structure with a hydroxyl group attached [27].

Lipid peroxidation could be roughly split into three stages, initiation, propagation, and termination [30]. At the initiation stage, a free radical encounter the lipid and produces a fatty acid radical. The fatty acid radical is unstable, easily propagating a chain reaction by reacting to nearby oxygen and creating another free radical. Finally, in the termination stage, the chain reaction ends naturally when all the free radicals react with one another, leaving behind serious damage to lipid structures such as cell membranes [2]. The peroxyl radical is the prominent cause for this disastrous chain reaction due to its low energy requirement to form anywhere in the body [25, 26, 30]. Vitamin E, especially alpha-tocopherol aim to target peroxyls and reduce them into hydroperoxyls by reacting to the peroxyl to donate a hydrogen atom to it, therefore neutralizing the radical [29].

Vitamin C:

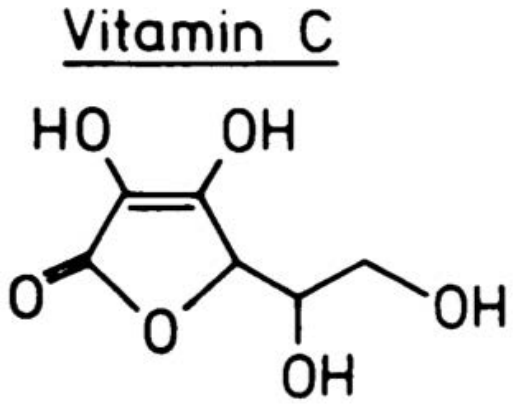


Figure 4. Model of the general structure of Vitamin C [29]

Vitamin C, also known as ascorbate acid, is a powerful antioxidant that is regarded as one of the most important substances for the body [27]. It is water soluble, meaning that it could exist in both intracellular and extracellular fluids [31]. Vitamin C could efficiently mop up superoxide, hydrogen peroxide, and more free radicals on its own, but it is also known to indirectly amplify the free radical scavenging properties of vitamin E as well. Studies have shown that vitamin C intake effects male sperm integrity too, suggesting DNA protective capabilities of vitamin C [27].

Vitamin C has redox properties which it utilizes to reduce free radicals to neutralize them, working much like what vitamin E does as vitamin C also possesses several hydroxyl groups on its ring structure to aid in the reactions [27]. The interesting part of vitamin C is that it does not work alone. The most pronounced collaboration between vitamins is the relationship between vitamin C and E. In vitro studies show that vitamin E existing within lipids would reduce a peroxide radical, then vitamin C will reduce the vitamin E to restore its antioxidating properties. As one of these vitamins is water soluble and the other is fat soluble, together they create a strong barrier against oxidation [26, 27, 31]. Other vitamins supplement the body by other methods. For example, vitamin D deficiency is associated with osteoporosis and osteomalacia [31], and vitamin K is associated with blood clots [31]. However, despite the promising sound of vitamins, the lifespan elongating effects of vitamins is largely debated, numerous experiments were conducted on mice in hopes to debunk the mystery surrounding vitamins, but the result are contrary. In eight studies reviewed in one paper, each giving mice a life-long sufficient supply of vitamin E and then comparing the mean age of the mice with a control group, the results were mixed. Only four shown a coherent increased lifespan, one with increased lifespan/no effect, two with no effect, and one even showing a decrease of mean lifespan. There are many factors leading to this discrepancy, the age when the vitamin treatment is initiated, the breed of mice, the dose of vitamin E, etc, and it is hard to pinpoint a defining factor [28, 32, 33]. Another study giving mice a life-long dose of vitamin C under cold-exposure to accelerate metabolism, but no significant increase to the mean age of the mice was observed compared to a control group. In fact, the researchers found that the group of mice given the vitamin C treatment had less gene expression of several genes linked to free radical scavenging, therefore concluding that whatever benefits vitamin C brought was offset by a decrease in endogenous protection, resulting in a net zero result, although the mechanisms are still unknown [34]. In short, vitamins are important for bodily functions, but acts strangely when it comes to longevity. One should still consume sufficient vitamins for their benefits, but do not have to overdo on this endeavor.

5. The Effects of Doing Sports on the Physical Health

Sports have a great influence on children, youth and old people. People who exercise regularly have enhanced nervous system regulation and are more agile and flexible. In addition, physical exercise can burn fat and increase muscle. Doing sports also can bring happiness to people and release the pressure.

For the elderly, doing a few exercises can improve and prevent joint pain, promote the action such as stomach.

5.1 Doing sports can improve our body function

Nowadays, the number of people having a sense of sports has increased. There are a lot of different kinds of sports, like swimming, running, playing football and so on. Swimming is a good way to prevent Cerebrovascular diseases. The heart rate of an average person is 70-80 / minute, and the output of each stroke is 60-80 milliliter. And the human heart rate that often swims can amount to 50-55 times/minute, a lot of outstanding swimmers, heart rate can amount to 38-46 times/minute, each stroke output quantity is as high as 90-120 milliliter. This shows swimming has a great impact on the heart. People who exercise swimming for a long time will have a significant increase in the volume of the heart, more powerful contraction.

In the case of regular swimming, the oxygen uptake per minute will increase, this is because blood vessel walls are thicker, more elastic and higher blood supply. Under normal condition, the heart rate of people who swim often is slower than people who never swim. For some old people, it's easy to get heart disease, Ischemia due to coronary artery, causing angina and heart attack. *For example, the percentage of people who have cardiovascular disease (CVD) at the age between 60-79 years old: 69.11% for men and 67.9% for women. There are 84.7% for men and 85.9% for women at the age of 80+.However the coronary arteries of swimming exercisers won't get narrower with age. There is enough blood to supply the heart muscle. Thus can prevent coronary heart disease. Pilates has become known in recent years as a combination of Chinese and Western fitness concepts. The purpose is to strengthen the body's core strength in conjunction with breathing, stretching the body and improving lumbar stability. [35] It is also being used as a training method for recovery in medicine and physical therapy. Pilates is a great help in stabilizing the spine. Muscles are needed to stabilize the spine. "One is the superficial core muscle group, mainly including the rectus abdominis, internal and external oblique, quadratus lumborum, erector spinae and hip muscle group. The other is the deep core muscle group, namely the local stable muscle group, which mainly includes multifidus muscle, transverse abdominis muscle, diaphragm muscle and pelvic floor muscle." Pilates strengthens muscles throughout the body, gives the spine the right movement pattern and improves muscular nerve control [36].

5.2 Reasonable and scientific exercise

Modern medical studies have found that people who exercise regularly are half as likely to die as those who exercise occasionally. At the same age, the extent of aging in people who exercise is slower than those who are not doing exercise, when the age increases, the gap will get bigger and bigger. For people who exercise infrequently and intensively, the body gets used to it. Because of the long interval time between exercises, each exercise is equivalent to starting from zero. We should exercise at least three times a week, allowing us to exercise a second time when our body is not fully recovered, which can make the exercise more effective. For those who cannot exercise for long periods of time or have no time. It's better to choose swimming, play golf and some other light exercises.

6. Conclusion

In conclusion, longevity is a complex process. Understandings on how life works updates quickly and there is no true underlying factor for longevity. Diet, lifestyle choices, living environment, genetics and more each play a leading role in this chaotic system, all having their own complications and uncertainties. The truth is that many pathways in the human-body are poorly understood, and we could only work with the data we have. Some relatively more promising fields of inquiry, especially with the rise of finer equipment, is study of genetics. Improvements in the understanding of genetics would lead help in the exploration of how these bodily mechanisms function, leading to innovation of brand-new products to aid in the human life experience.

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