Chapter

The Centenarians: An Emerging Population

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Abstract

Long life is a topic of great interest in medicine and among the general public. The "successful aging" which is a high priority for individuals and societies, is aging without any disabilities and severe diseases. In several countries, the increase in life expectancy has led the very old to become the fastest growing segment of the population. Centenarians are subjects living 100 years or older. The majority of centenarians are females (female to male ratio around 3.6/1). A very small fraction of centenarians (up to 0.5%) will live 110 years or older (supercentenarians). Most centenarians have managed to avoid, postpone, or overcome the important age-related and life-threatening diseases and disabilities (e.g., ischemic heart disease, stroke, chronic obstructive pulmonary disease, cancer, respiratory infection, type 2 diabetes, osteoporosis, and dementia). Some forecasts suggest that most babies born in developed countries since 2000 will become centenarians. In 2020, the number of centenarians in the world was approximately 573,000, mainly from the United States of America (USA). This number could reach approximately 3,676,000 by 2050. In the absence of the genetic predisposition to become centenarian, there are several ways to extend longevity (e.g., lifestyle, reduction of several life-threatening diseases and disabilities, hormonal replacement or blockade, antioxidants, maintenance of a proper autophagic activity, stem cell therapy, and gene therapy). The continuous increase of the number of centenarians has worldwide practical implications including profound impact on intergenerational interactions and significant financial challenges for any society, especially in relation to medical expenses.

Keywords: centenarians, supercentenarians, longevity, genetics, emerging population

1. Introduction

Long life is a topic of great interest in medicine and among the general public. In several countries, the increase in life expectancy has led the very old to become the fastest growing segment of the population [1–4]. Centenarians are subjects living 100 years or older. Most centenarians have managed to avoid, postpone, or overcome the important age-related and life-threatening diseases [3, 5, 6].

The continuous increase of the number of centenarians has worldwide practical implications including profound impact on intergenerational interactions and significant financial challenges for any society, especially in relation to medical expenses.

2. Aging and lifespan

Aging is a natural universal phenomenon affecting all living organisms (e.g., plants, animals, and humans). It is a progressive deterioration of the cell and organ functioning due to damage accumulation over time. The exact underlying mechanisms of aging at the cellular level are not fully understood. The most popular theory is the free radical theory [7].

Lifespan is a biological characteristic of every species. However, it can be modified by mutations or by a variety of interventions (e.g., lifestyle, pharmacological, stem cell, and genetic interventions) [8–24].

Lifespan of living organisms ranges from few hours (animals) to few thousand years (plants). Phenotypic plasticity can affect the long lifespan of both plants and animals [25].

2.1 Plants

The lifespan in plants ranges from few weeks to few thousand years. Bristlecone pine (*Pinus longaeva*), a tree found in the higher mountains of California (USA), is among the plants with the longest lifespan (around 5,000 years) (**Figure 1**).

Figure 1.
Bristlecone pine (Pinus longaeva) can live around 5,000 years (Picture downloaded from the internet "Google Images").

2.2 Animals

The lifespan in animals is between few hours to few hundred years. The shortest lifespan is seen with mayfly (up to 24 hours). The longest lifespan is observed with clam (more than 400 years). Ming the clam was the oldest clams ever discovered (507 years old). Ming was accidentally killed in 2006 during a fact-finding mission (**Figure 2**).

Figure 2.
Ming the clam lived 507 years (Picture downloaded from the internet "Google Images").

2.3 Humans

The theoretical lifespan in humans is around 120 years. However, very few individuals reach this theoretical age since several events can impact longevity (e.g., diseases, suicide, accident, and war).

Human aging results from accumulation of genetic, molecular, and cellular damages. It is a multifactorial process. There are several theories explaining the aging phenomenon. The most wildly accepted theory of aging is the free radical theory [7]. According to this theory, continuous, unrepaired oxidative damage of macromolecules constitutes the molecular basis of aging.

Aging and lifespan are influenced by multiple factors including genetic, epigenetic, lifestyle, environmental, metabolic, and endocrine factors [3, 8–14, 21, 26–41].

Extending longevity while keeping health and vitality has been a dream for mankind since ancient times. The "successful aging" which is a high priority for individuals and societies, is aging without any disabilities and severe diseases [42, 43]. The fountain of youth is a mythical spring capable of restoring the youth of anyone who drinks or bathes in its water (**Figure 3**).

Figure 3.
The fountain of youth (from Erhard Schön, 1525) is a mythical remedy to aging (Picture downloaded from the internet "Google Images").

2.3.1 Physiological changes associated with aging

With aging, there is a gradual, time-dependent, and heterogeneous decline of physiological functions (**Figure 4**). The human body goes through multiple physiological changes including an overall decrease in the size of organs (e.g., brain shrinkage), endothelial pro-atherosclerotic changes, ovarian atrophy, osteopenia (predominantly in women), sarcopenia (mainly in the lower body), adipose tissue enlargement (mostly visceral fat), and skin atrophy (especially in women) (non-exhaustive list) [9, 10, 32, 41]. Some changes are very subtle (within normal ranges) with no or unknown clinical consequences. Lifestyle conditions (e.g., diet, exercise, and medications) and environmental factors (e.g., noise, temperature, and air quality) can delay or potentiate these changes.

Autophagy ("self-eating") is a major protein turnover pathway where cellular components are delivered into the lysosomes for degradation and recycling. It maintains cellular homeostasis under stress conditions. The autophagic activity decreases in aging individuals [21].

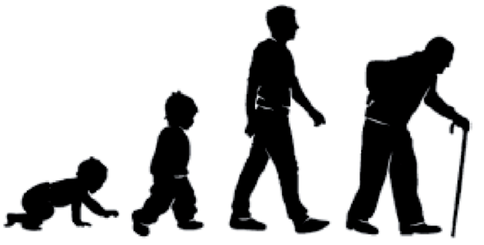

Figure 4.
Aging is associated with a gradual decline of different functions and performances (Picture downloaded from the internet "Google Images").

Mitochondria are major contributors to the maintenance of energy homeostasis. They are important sources of reactive oxygen species (ROS) generation. ROS can cause oxidation of macromolecules including DNA. Aging subjects have progressive mitochondrial decline [10, 11, 39, 44].

Aging is associated with a mild inflammatory state that is sometimes referred to as "inflammaging". This inflammatory state is characterized by increased blood levels of several adipokines (e.g., interleukin 6 and tumor necrosis factor alpha). Environmental factors can further modify the inflammatory state of aging [32].

Multiple endocrine changes occur with aging, affecting the body functions [9, 10, 12, 31, 35–37, 39–41, 45–49]. The hypothalamus, an endocrine structure located in the brain that is a master regulator of multiple hormonal secretion, plays a central role in aging. With aging, the sensitivity of the hypothalamus to different feedback signals decreases [36]. Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels decline during aging [37]. According to most studies, free triiodothyronine (T3) levels decrease while reverse T3 (rT3) and thyroid-stimulating hormone (TSH) levels increase [45–47] with aging. Significant hormonal change occurs in women at menopause with important reduction in estrogen (E) levels [48]. In men, testosterone (T) levels decrease gradually with age [40]. There is an important decrease in dehydroepiandrosterone (DHEA) levels in aging individuals [49]. Adipose tissue, which is the largest endocrine gland, secretes several adipokines. With aging, there is an increase in the levels of most adipokines (e.g., leptin, resistin, interleukin 6, tumor necrosis factor alpha, and adiponectin) [41].

The relevant metabolic/hormonal changes during normal aging are reported in **Table 1**.

Parameter	**Change**
Mitochondrial activity	Decrease (gradual)
Autophagic activity	Decrease (gradual)
Inflammatory state	Increase (gradual)
GH	Decrease (gradual)
IGF-1	Decrease (gradual)
T3	Decrease (gradual)
rT3	Increase (gradual)
TSH	Increase (subtle, at old age)
E (females)	Decrease (abrupt, at menopause)
T (males)	Decrease (gradual)
DHEA	Decrease (gradual)
Adipokines	Increase (gradual)
Insulin resistance	Increase (gradual)

Table 1.
Relevant metabolic/hormonal changes during normal aging.

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2.3.2 Genetic and epigenetic factors affecting aging and lifespan

Genes play an important role in the regulation of aging and lifespan [3, 8, 10, 27–29, 31, 50]. Extensive number of genes (between 300 to over 700 genes) have been listed [28, 29]. Genes include *APOE1*, *ATM*, *BCL*, *CETP*, *FOXO3A*, *HSPA*, and *TERC* (non-exhaustive list). Genetic factors that are associated with longevity are heritable [27]. Several endocrine and metabolic pathways are linked genetically with aging and contribute to different phenotypes [31]. Multiple gene mutations leading to delayed aging and increased lifespan have been discovered over the last three decades. Many of the affected genes are components of endocrine-signaling pathways (e.g., GH and IGF-1 pathways).

A dramatic example of genetic impact on aging and lifespan is observed with Hutchinson-Gilford progeria syndrome, a rare sporadic, autosomal dominant syndrome that causes premature aging. In most cases, the disorder is due to a mutation characterized by a change from glycine GGC to glycine GGT in codon 608 of exon 11 of the lamin A (*LMNA*) gene causing the production of an abnormal lamin A (progerin). Progerin accumulates in cells' nuclei and exerts multiple toxic effects [50]. The affected individuals generally die from myocardial infarction or stroke around a mean age of 15 years (**Figure 5**).

Epigenetic processes also influence aging and lifespan [8, 9, 11, 26, 30].

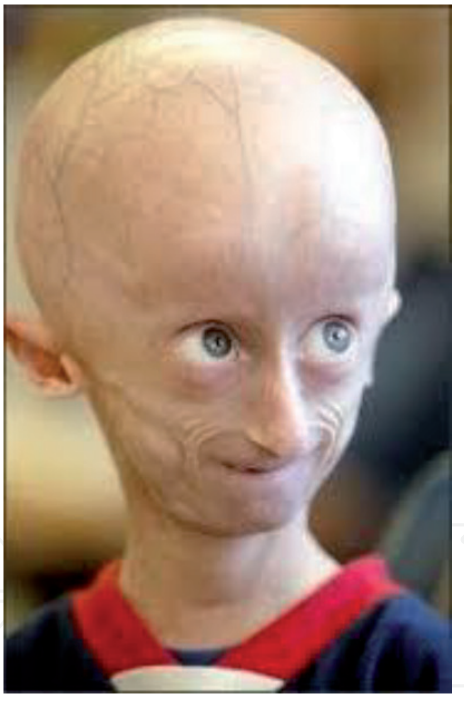

Figure 5.
Subject with premature aging due to Hutchinson-Gilford progeria syndrome (Picture downloaded from the internet "Google Images").

2.3.3 Lifestyle and environmental factors affecting aging and lifespan

Lifestyle (e.g., diet, sleep, smoking, exercise, stress, and medications) and the environment (e.g., household, social condition, noise, temperature, and air quality) play an important role in the aging process and lifespan (**Figure 6**) [8, 9, 26, 51].

Caloric restriction, physical fitness, and good air quality can delay aging and increase lifespan. Conversely, excessive food consumption, sedentary lifestyle, and air pollution will have a negative impact on aging and lifespan.

Figure 6.
Lifestyle and environmental factors can affect aging and lifespan (Picture downloaded from the internet "Google Images").

2.3.4 Metabolic factors affecting aging and lifespan

Metabolic factors play an important role in the aging process and lifespan (**Figure 7**) [10, 11, 21, 33, 34, 39, 41, 44].

The decrease in autophagic activity observed with aging contributes to accumulation of damaged macromolecules and organelles. It can aggravate age-associated diseases and, therefore, shorten lifespan [21].

Mitochondria play a key role in several theories of aging. The reduction in mitochondrial activity with aging can impact lifespan [10, 11, 39, 44].

The inflammatory state associated with aging is responsible for insulin resistance. Insulin resistance is a risk factor for the development of several chronic disorders (e.g., obesity, type 2 diabetes, and ischemic heart disease) that are influencing aging and lifespan [10, 14, 42].

The amount of body fat influences health and lifespan. Both insufficient or excess body fat as observed in subjects with underweight or overweight/obesity have been reported to be associated with increased mortality and reduced lifespan [33, 34, 41].

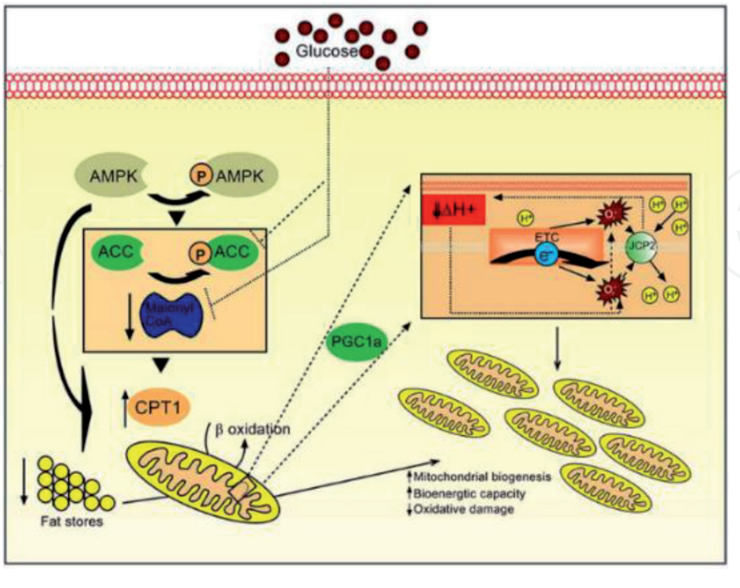

Figure 7.
Metabolic factors impact aging and lifespan (Picture downloaded from the internet "Google Images").

2.3.5 Endocrine factors affecting aging and lifespan

Hormones influence the aging process and lifespan (**Figure 8**) [9, 10, 12, 13, 31, 35–41, 45–49, 52–54]. Several endocrine-signaling changes occur during normal aging. Some hormonal changes may be beneficial while others can be harmful. The role of GH in aging and lifespan has been reported in several studies [37, 38, 52]. Reduced GH may lead to delay aging and increased lifespan while excess GH can have the opposite effects. GH secretion rate in offspring of long-lived families is lower than controls. Thyroid hormones play an important role in aging and lifespan. There is a negative correlation between thyroid hormone levels and lifespan [39]. The timing of menopause, a physiological condition occurring in women around the age of 50 years and associated with important decrease in E levels, may affect lifespan [48]. Indeed, E replacement therapy can reduce mortality (increase of lifespan) in post-menopausal women younger than 60 years [13]. In men, low T levels are associated with increased mortality [40]. Treatment with DHEA decreases insulin resistance and inflammatory adipokines and may positively impact lifespan [53]. The elevated levels of pro-inflammatory adipokines (e.g., interleukin 6 and tumor necrosis factor alpha) can negatively impact aging and lifespan. Elevated levels of adiponectin (anti-inflammatory adipokine) may be beneficial and associated with increased lifespan [41, 54].

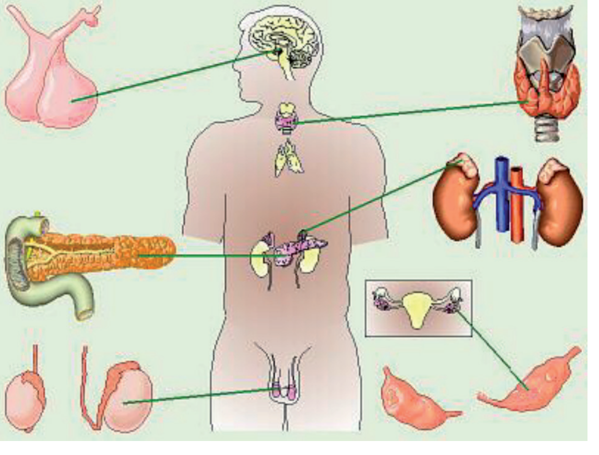

Figure 8.
Endocrine factors influence aging and lifespan (Picture downloaded from the internet "Google Images").

2.3.6 Disease occurrence with aging

The "successful aging" is aging without any disabilities and severe diseases (extension of healthspan) [42, 43]. It is more important to promote healthier aging than better treat age-related diseases.

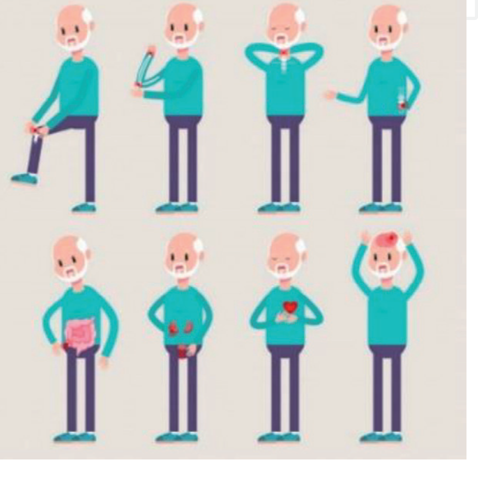

Figure 9.
Multiple organs can be affected in aging subjects (Picture downloaded from the internet "Google Images").

Several geriatric syndromes (e.g., frailty) and diseases (e.g., cardiovascular disease) occur with aging and affect quality of life and longevity [19, 42]. The incidence of adult diseases increases with age. In subjects older than 60 years, the most common age-related and life-threatening diseases and disabilities are ischemic heart disease, stroke, chronic obstructive pulmonary disease, cancer, respiratory infection, type 2 diabetes, osteoporosis, and dementia (non-exhaustive list) [14, 42]. The majority of older people may have more than one disorder. The incidence of multimorbidity (e.g., three or more diseases) increases exponentially with aging (**Figure 9**) [15]. For several of these conditions, the burden is greater in low-income and middle-income countries [42]. Some diseases (e.g., thyroid diseases) may have subtle symptoms that can be attributed to normal aging [55].

2.3.7 Life expectancy

At the beginning of the 20th century, life expectancy in most developed countries was between 45 and 50 years. Over the last several decades, there has been a gradual increase in life expectancy in most countries [27, 56]. The study of mortality and life expectancy in 195 countries and territories showed that globally, between 1950 and 2017, life expectancy increased from 48.1 years to 70.5 years for men and from 52.9 years to 75.6 years for women [56].

In less developed countries, the increase in life expectancy is mainly the result of reduced mortality at younger ages. In high-income countries, the increase in life expectancy is mainly due to rising life expectancy in subjects who are 60 years or older.

The increase in life expectancy together with the decrease in fertility rates are leading to the rapid aging of populations around the world. This has important demographic and socio-economic consequences worldwide.

3. Centenarians

Centenarians are subjects living 100 years or older. They represent a model of successful aging [3, 5, 6]. Semi-supercentenarians are those who reach an age of 105–109 years. A very small fraction of centenarians (up to 0.5%) will live 110 years or older (supercentenarians) [5, 30].

3.1 Prevalence

The total world population is currently around 7.8 billion and is projected to reach 9.9 billion by 2050. In several countries, the increase in life expectancy has led the very old to become the fastest growing segment of the population [1–4]. Some forecasts suggest that most babies born in developed countries since 2000 will become centenarians.

Estimates of the centenarian population can be difficult since some centenarians do not have birth records to confirm their age. According to United Nations estimates, in 2020, the number of centenarians in the world was approximately 573,000. This number was approximately 34,000 in 1950 and could reach approximately 3,676,000 by 2050.

3.1.1 Prevalence by gender

The majority of centenarians are females. The female to male ratio is currently around 3.6/1 and is expected to be approximately 2.9/1 by 2050 (**Figure 10**).

Figure 10.
Centenarians are mainly females but the female to male ratio is gradually decreasing (Picture downloaded from the internet "Google Images").

3.1.2 Prevalence by country

Currently, USA has the highest number of centenarians, followed by Japan, China, India, and Italy. Japan and Italy have the highest proportion of centenarians to the total population. By 2050, China is expected to have the largest centenarian population, followed by Japan, USA, Italy, and India (**Table 2**).

Country	Last Reported Number (Year)	Expected Number by 2050
World	**573,000 (2020)**	**3,676,000**
USA	97,000 (2020)	378,000
Japan	80,000 (2020)	441,000
China	48,000 (2015)	620,000
India	27,000 (2015)	207,000
Italy	25,000 (2015)	216,000

Table 2.
Number of centenarians worldwide and in top five countries (United Nations and national sources).

The oldest supercentenarian with well-documented age was Jeanne Louise Calment (1875–1997) from Arles, France who lived 122 years (**Figure 11**). She married at the age of 21 years, had one pregnancy (gave birth to a girl), and never worked. With the exception of migraines and bilateral cataracts, she was quite healthy and remained mentally sharp until the end of her life. She did daily gymnastics and was socially active. She never took any medication apart from aspirin for migraines. She enjoyed chocolate, drank a small daily amount of wine, smoke a cigarette after each meal, and took a nap in the afternoon. She also had a good sense of humor. To the question "Why do you live so long?", she replied "Because God has forgotten me".

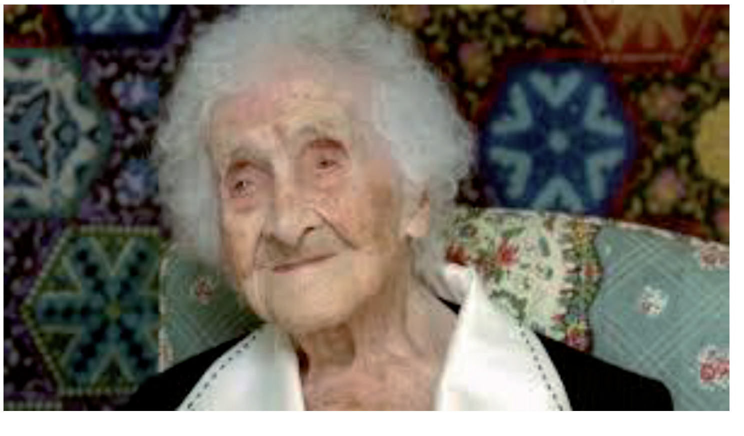

Figure 11.
Jeanne Louise Calment from Arles, France (1875–1997), the oldest confirmed supercentenarian who lived 122 years (Picture downloaded from the internet "Google Images").

3.2 Physiological profile

Maintenance of a proper autophagic activity may contribute to extended longevity. Healthy centenarians have autophagy augmentation as reflected by increased levels of beclin-1, a key regulator of autophagy [57].

Lower thyroid hormone levels and higher TSH levels have been reported to be associated with increased longevity [31, 39, 45–47]. Centenarians have higher TSH levels compared to controls, partly due to a genetic background [31].

Adiponectin levels are elevated in centenarians and associated with a favorable metabolic phenotype. They may contribute to extended longevity [41, 54].

Frailty plays an important role in health outcomes and mortality. A study of Chinese centenarians demonstrated that centenarians are frailer than younger elders. Management of frailty can help achieving healthy longevity [58]. A study of centenarians living in New York City (USA) showed that despite reduced levels of physical functioning and social resources, centenarians were in good mental health suggesting high resilience and ability to adapt to age-associated challenges [59].

3.3 Genetic/epigenetic profile

There is a strong genetic influence in subjects with extreme longevity (**Figure 12**) [3, 8, 10, 27, 31]. Genetic component may include several genetic modifiers each with modest effects, but as a group, they can have a strong impact [27]. Several genotypes known to influence longevity are enriched in centenarians (e.g., *CETP-VV* and *FOXO3A-T*) [10]. Homozygosity in the 405*VV* variant of *CETP* (cholesterol ester transfer protein) gene is associated with lower concentrations of CETP, higher concentrations of high-density lipoprotein (HDL) cholesterol, and larger HDL particle size, all associated with protection against ischemic heart disease and Alzheimer disease. *FOXO3A* (forkhead box O3A) gene is a member of a family of transcription factors mediating insulin action and stress resistance. Several gene mutations responsible of extended longevity are components of endocrine-signaling pathways. For example, centenarians have a variety of genetic alterations in the GH/IGF-1 pathway causing reduced function of GH/IGF-1 pathway that is associated with protection from aging.

Epigenetic processes might also play a role in extreme longevity [8, 9, 11, 26, 30].

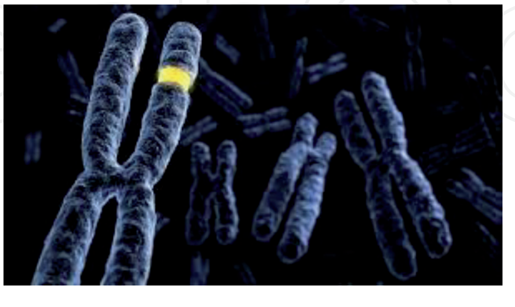

Figure 12.
Several longevity genes are enriched in centenarians (Picture downloaded from the internet "Google Images").

3.4 Lifestyle and environmental characteristics

Lifestyle is an important signature of healthy aging and extreme longevity [26]. There are significant lifestyle (e.g., diet) and cultural (e.g., social life) differences between the native of the top five countries (e.g., USA, Japan, China, India, and Italy) that have the highest numbers of centenarians. However, centenarians share similarities for several lifestyle characteristics (**Figure 13**). The global calorie ingestion is reduced in centenarians in comparison to younger elders. Most centenarians have a plant-based diet, rich in vegetables, fruits, and oils, and usually a restricted intake of dairy products, red meat, and poultry [60]. A study of lifestyle of centenarians living in Zhejiang Province (China) showed significantly higher consumption of fruits, coarse cereals, and pasta, and lower percentage of smoking and engagement in daily recreational activities (watching television, listening to radio) compared to non-centenarians [61].

Additional important lifestyle and environmental characteristics of centenarians are the presence of physical and mental activities (with daily objectives), psychological resilience, optimism, flexibility, and life in small towns with little pollution and significant social relationships. A study of health and functional status of Japanese centenarians suggested that maintenance of physical independence is a key factor of survival into extreme old age [62].

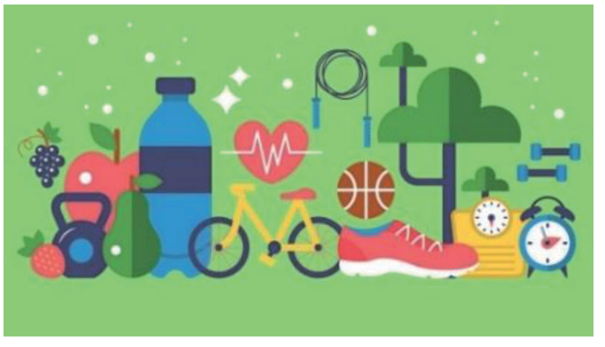

Figure 13.
Centenarians have several common lifestyle characteristics (Picture downloaded from the internet "Google Images").

3.5 Disease occurrence and mortality

Centenarians have variable clinical conditions. Some may have multimorbidity while others have no significant diseases. However, some of the "healthy" centenarians have signs of advanced aging (e.g., visual disorder, hearing loss, and limited locomotor capacity). Centenarian men tend to have better cognitive and physical functional status than centenarian women [3].

Most centenarians have managed to avoid ("escapers"), postpone, or overcome ("survivors") the important age-related and life-threatening diseases and disabilities (e.g., ischemic heart disease, stroke, chronic obstructive pulmonary disease, cancer, respiratory infection, type 2 diabetes, osteoporosis, and dementia) [3, 5, 6]. Supercentenarians can compress morbidity and disability to the very ends of their lives.

A study assessing the place and cause of death of centenarians in England showed that centenarians more likely die of old age/frailty and respiratory infection and less likely of ischemic heart disease and cancer compared to younger elders [4]. Centenarians are relatively protected from cancers (lower incidence, lower metastatic rate, lower mortality). It has been hypothesized that the tumor suppressor gene p53 is a key element in protecting centenarians from cancers [6]. In Spanish centenarians, the likelihood of having the wild-type genotype of *GSTT1*, which is associated with lower cancer risk, was found to be higher than control, young subjects [63]. The top cancers in centenarians are breast, colorectal, prostate, and lung cancers [64].

The main causes of mortality in centenarians compared to younger elders are reported in **Table 3**.

Condition	Mortality Rate	
	Younger Elders	Centenarians
Old age/frailty	1%	28%
Respiratory infection	6%	18%
Ischemic heart disease	19%	9%
Cancer	25%	4%

Table 3.
Main causes of mortality in centenarians compared to younger elders.

4. Interventions to extend longevity

In the absence of the genetic predisposition to become centenarian, there are several potential ways to extend longevity and eventually surpass 100 years. The potential tools that can be proposed to extend longevity include lifestyle, reduction of several life-threatening diseases and disabilities, hormonal replacement or blockade, antioxidants, autophagy inducers, senolytic drugs, stem cell therapy, and gene therapy [8–24, 26, 33–35, 39, 41, 42, 51, 53, 65, 66].

4.1 Lifestyle

Diet rich in vegetables, fruits, fibers, and poor in saturated fat and red meat, even if associated with sarcopenia, may extend longevity [26, 65]. Anti-inflammatory diets like Mediterranean diet are associated with reduced mortality from cardiovascular disease. Drinks containing sugar and alcohol consumption should be limited, and smoking avoided.

Based on animal data, it has been proposed that even in normal weight individuals, caloric restriction (cutting approximately 500 calories/day) without causing malnutrition and subsequent sarcopenia and osteopenia may improve health and extend longevity [8–11, 21, 26, 33, 35, 39, 66]. However, long-term prospective studies in humans are needed to confirm the benefits of this approach. Hypocaloric diet should be implemented in case of overweight or obesity.

Regular exercise can add few more years to life expectancy. Physical fitness is an important predictor of mortality and being able to live an independent life at old age. Potentiation of physical fitness is a valuable anti-aging therapy [11, 51].

In addition, living in a clean and stress-free environment, being mentally active with positive attitude, having daily objectives, and involved in social interactions further contribute to extended longevity.

4.2 Reduction of life-threatening diseases and disabilities

Overweight and obesity should be prevented or managed with appropriate tools (e.g., diet, exercise, drugs, medical devices, and surgery) to decrease comorbidities and mortality [33, 34, 41].

Reduction of other life-threatening diseases and disabilities that can affect longevity (e.g., ischemic heart disease, stroke, chronic obstructive pulmonary disease, cancer, respiratory infection, type 2 diabetes, osteoporosis, and dementia) with lifestyle, drugs, and surgery can improve the quality of life and extend longevity [14, 15, 42].

4.3 Hormonal replacement or blockade

Considering that some hormonal changes during aging are beneficial while others are harmful, it is tempting to use hormonal replacement or blockade to extend longevity [12, 13, 53].

GH represents an interesting and intriguing example in this regard. Although GH promotes health and vitality in young subjects and it is well established that its levels decrease with aging, several studies suggest that reduced GH can be more beneficial for overall health and longevity than excess GH [37, 38, 52]. This discourages the use of GH as an anti-aging treatment. However, additional clinical studies are needed for a definitive conclusion on the role of GH/IGF-1 axis in aging [10].

E replacement therapy in post-menopausal women younger than 60 years has been reported to reduce mortality (extension of longevity) [13].

Treatment with DHEA has beneficial effects on insulin sensitivity (increase) and inflammatory adipokines (decrease) [53]. This can potentially reduce morbidity and mortality.

4.4 Antioxidants

Free radical theory is an important theory of aging [7]. Oxidative stress significantly influence the aging process and longevity. The use of antioxidants to combat aging has received considerable interest [16]. Several antioxidants (e.g., resveratrol and curcumin) are currently under investigation.

4.5 Autophagy inducers

Defects in autophagy have been linked to several diseases that can impact aging and lifespan. Maintenance of a proper autophagic activity with autophagy inducers has the potential to extent longevity [16, 20, 21]. Autophagy inducers include non-pharmacologic tools (e.g., caloric restriction and exercise) and several nutritional supplements and approved drugs (e.g., vitamin D, resveratrol, metformin, and rapamycin) (non-exhaustive list). Novel and more specific autophagy-inducing drugs are under investigation.

4.6 Senolytic drugs

Senescence is a common feature occurring in several tissues and organs during the aging process. Senotherapy represents a promising new therapeutic area [16, 19, 22, 23]. Senolytics are a class of drugs (e.g., dasatinib, quercetin, fisetin, and navitoclax) that selectively clear senescent cells. Several clinical studies are currently planned or ongoing. Results from early pilot studies suggest that senolytic drugs can decrease senescent cells, reduce inflammation, and alleviate frailty.

4.7 Stem cell therapy

Stem cell therapy represents a new emerging era in medicine (**Figure 14**) [16–18]. It has the potential to delay the aging process and, therefore, extend longevity, by better treating chronic diseases and degenerative conditions that impact lifespan.

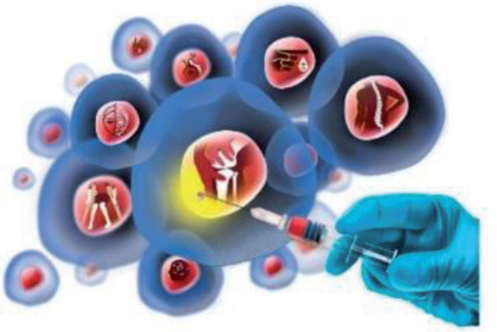

Figure 14.
Stem cell therapy has the potential to delay the aging process and extend longevity (Picture downloaded from the internet "Google Images").

4.8 Gene therapy

Genes are promising research targets to delay the aging process and extend longevity (**Figure 15**) [24]. Gene therapy allows the modulation of the genome architecture using both direct (by gene editing) and indirect (by viral or non-viral vectors) approaches. However, these genetic interventions may be difficult to implement in humans without knowing all the potential health consequences during an entire life.

Figure 15.
Genes can be targeted to delay the aging process and extend longevity (Picture downloaded from the internet "Google Images").

5. Consequences of extended longevity

Over the past three decades, the number of very old individuals, especially centenarians, has increased significantly. This has created (and will continue to create) challenges at the individual, family, and societal levels.

5.1 Individual aspects

With the availability of many extra years to live and if health permits, subjects may want to delay retirement age, continue education, undertake a new career, or pursue a passion (**Figure 16**).

Figure 16.
Healthy elderly can benefit from additional education and job opportunities (Picture downloaded from the internet "Google Images").

5.2 Family aspects

Some centenarians have extended family over multiple generations. These individuals can enjoy interactions with their children, grandchildren, and great-grandchildren at different stages of their life (**Figure 17**).

Figure 17.
Centenarians can enjoy multigenerational family interactions (Picture downloaded from the internet "Google Images").

5.3 Societal aspects

There is an urgent need to assess the key characteristics of very old individuals, especially centenarians, across countries to better serve these populations and ensure a high quality of life in their remaining years [1, 2]. There is a requirement for nursing care at home or hospital. Increasing care home bed capacity could reduce dependence on hospital care at the end of life [4, 59].

The payment of pension and social security benefits to a growing number of very old subjects for several decades is a heavy financial challenge for any society. With extended longevity, there is an increasing number of subjects treated for at least three different diseases with at least three different treatments [15]. This will have a significant financial impact for the society (**Figure 18**). However, this situation may not be applicable to all centenarians since some have managed to avoid, postpone, or overcome several important age-related diseases and disabilities.

Figure 18.
Centenarians expose societies to financial challenges (Picture downloaded from the internet "Google Images").

6. Conclusions

Long life is a topic of great interest in medicine and among the general public. The increase in life expectancy has led the very old to become the fastest growing segment of the population in several countries.

Centenarians are subjects living 100 years or older. The majority of centenarians are females and a very small fraction of centenarians are supercentenarians.

Most centenarians have managed to avoid, postpone, or overcome the important age-related and life-threatening diseases (e.g., ischemic heart disease, stroke, chronic obstructive pulmonary disease, cancer, respiratory infection, type 2 diabetes, osteoporosis, and dementia).

The continuous increase of the number of centenarians has worldwide practical implications including profound impact on intergenerational interactions and significant financial challenges for any society, especially in relation to medical expenses.

Conflict of interest

The author declares no conflict of interest.

Dedication

The author is dedicating this chapter to his paternal great-grandfather, Abdolrahim Heshmat (1841–1951), a supercentenarian from Shiraz, Iran who lived 110 years.

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