7-2019

Updated Genes, Lifestyles, and their Interactions for Human Longevity

Chun Xu
The University of Texas Rio Grande Valley

Brenda Bin Su
The University of Texas Rio Grande Valley

Alexis Villafranca
The University of Texas Rio Grande Valley

Chunxiang Mao
The University of Texas Rio Grande Valley

Stephanie Hernandez
The University of Texas Rio Grande Valley

See next page for additional authors

ECRONICON OPEN ACCESS

EC NEUROLOGY
Research Article

Updated Genes, Lifestyles, and their Interactions for Human Longevity

Brenda Bin Su[2,3,4], Alexis Villafranca[1], Chunxiang Mao [1], Stephanie Hernandez[1], Stephanie Lozano[1], Masoud M Zarei[1], KeSheng Wang[5], Saraswathy Nair[1] and Chun Xu[1]*

[1]*Department of Health and Biomedical Science, University of Texas, Rio Grande Valley (UTRGV) Biomedical Science, UTRGV, USA*

[2]*Department of Molecular Science, School of Medicine, UTRGV, USA*

[3]*Chinese Medical Center, Dubai, United Arab Emirates*

[4]*Ontario College of Traditional Chinese Medicine, Ontario, Canada*

[5]*Department of Biostatistics and Epidemiology, College of Public Health, East Tennessee State University, Johnson City, USA*

***Corresponding Author:** Chu Xu, Department of Health and Biomedical Sciences, College of Health Professions, University of Texas Rio Grande Valley, Brownsville, TX, USA.

Received: May 21, 2019; **Published:** July 01, 2019

Abstract

Healthy aging is the prolonging of optimal wellbeing during the progressive decline in physiological functions that are necessary for survival. Two important components of aging include an individual's genetic makeup and lifestyle choices such as diet and exercise. Genetic factors are responsible for the functional physiology of the body including cell maintenance, metabolism and apoptosis. The individual effects of genes and lifestyle choices on aging are reported mainly in Caucasian populations, with very limited studies in minority populations. In this review, we included the effects of genes and environment and the interaction between them on aging in Hispanic population in addition to other populations.

Our systematic review focuses on exploring present findings that assess the involvement of genes and lifestyles with healthy aging, as well as the interactions between the two. The purpose of the review is to update current findings of longevity as it pertains to the genetic composition of humans and the lifestyle choices people make. We were specifically looking for research conducted in the US Hispanic population and/or other minority populations. We searched through PubMed to identify reliable and relevant research articles involving 'genes', 'lifestyle', 'longevity', and 'healthy aging'. We filtered the articles for those that pertain towards humans and are in the English language.

We searched most updated top longevity-associated genes, lifestyles, and their interactions. We found that the biological and environmental factors (e.g., lifestyle) involved in aging are important factors that attribute towards attainment of longevity.

The individual's genetic composition and lifestyle choices significantly impact the aging process and longevity.

Keywords: *Longevity; Lifestyles; Genes; Interactions of Lifestyle and Genes*

Abbreviations

TNF: Tumor Necrosis Factor; CVD: Cardiovascular Diseases; DASH: Dietary Approaches to Stop Hypertension; aMED: Alternate Mediterranean Diet Score; EL: Exceptional Longevity; BP: Blood Pressure; BELFAST: Belfast Elderly Longitudinal Free-living Ageing Study

Introduction

Aging is the progressive decline in physiological functions that are necessary for survival. This decline in function occurs at the cellular and molecular levels, and leads to an increase in susceptibility to diseases with eventual death [1]. Longevity pertains to the duration of a

person's life. However, longevity does not necessarily mean that the person has lived a long and healthy life. Healthy aging involves living through a long period while maintaining a person's wellbeing. Therefore, our review focuses on the healthy aging of elderly people to obtain optimal health into old age.

Through the centuries, the science behind aging and the theories as to how to prevent the aging process have been contemplated. Over the past twentieth century, life expectancy has increased substantially due to public health efforts and modern technology [2]. On average, the United States life expectancy is 78.8 years in 2017 [3] as compared to a century ago in 1917 where the life expectancy was 50.9 years [4]. However, increases in life expectancy have only led us to have more control over infectious and acute diseases. The top ten leading causes of death in the United States involve mainly chronic diseases [5]. Therefore, elderly people are living into their 70's and 80's, but the majorities are suffering from at least one chronic disease. This hinders their independence, security, and productivity into old age.

Human life expectancy is thriving, so the attainment for healthy aging is growing in popularity. Aging is complex, and its multifactorial process is not completely understood. There are multiple theories as to what leads to the aging of the human body [6]. However, two known important aspects include a person's genetic profile and the lifestyle choices over his/her lifetime reported mainly in Caucasian populations. It is estimated that genes account for about 25 - 40% of the variation in human longevity and another ~50 - 60% is anticipated to be due to lifestyle choices [7,8]. We will focus on how lifestyle choices, genes, and the interaction between the two correspond to longevity in four populations, including Caucasian, Hispanic, African and Asian populations. Our objectives include that individual effects of genes and lifestyle choices on aging are reported mainly in Caucasian population, with very limited studies in minority populations. Thus, we conducted systematic review and collected updated top longevity-associated genes, lifestyles, and their interactions on minority populations in addition to the Caucasian population.

Lifestyles

Lifestyle choices fall under the non-genetic category involved with aging, and are personal decisions, a person makes about how to live and behave. These decisions affect a person's health and wellbeing. Lifestyle choices incorporate a large range of factors. These factors may include many, however, we are interested in smoking, alcohol intake, nutrition, exercise, stress, weight, and sleep, which have been well documented and studied in different populations. These factors are daily choices a person can make, and can have important effects on a person years down the road [9]. Therefore, their impacts on longevity is critical.

It is important to understand that certain unhealthy lifestyle choices such as smoking, large amounts of alcohol intake, poor diet, and lack of exercise are underlying factors for premature death due to chronic diseases. These chronic diseases include diabetes, chronic obstructive pulmonary disease, cirrhosis, heart disease, and many cancers reported in the Centers for Disease Control (CDC) and Prevention Mortality Report [5]. The consequences of living an unhealthy lifestyle over a long period can lead to chronic diseases and reduced life expectancy.

On the contrary, healthy lifestyle choices are proven to prolong life in a healthy manner. Healthy lifestyle choices would involve eating a well-balanced diet, exercising regularly, not smoking, getting enough sleep, minimal stress, and having limited alcohol intake. These are decisions that will lead to having a healthy body and mind into old age and prevent chronic diseases [6]. The benefits of living a healthy lifestyle during a person's time as a young individual are related to the health and wellbeing of an individual once he/she reaches older age. They will be living a much more self-reliant and active life in old age as compared to individuals who have made unhealthy lifestyle choices and must depend on modern medical assistance and medication to live a quality lifestyle.

Genes

Aging involves the decline in molecular and cellular function. These molecular errors can occur over a person's lifetime due to the individual's genetic composition. Genes play a critical role in longevity, as they can either help an individual live longer or shorter over the individual's lifetime, specifically when people get older than 85 years of age [10]. For example, Tumor Necrosis Factor (TNF) gene has

been reported to be associated with an increased life - expectancy over 88 years in males [11]. The APOE gene, specifically its ε 4 allele, has shown its negative impact on longevity. Studies show that people, who live longer and healthier lives, have low frequency of the APOE ε 4 allele than those who died at a younger age. This is due to the fact that the ε 4 allele is associated with increased plasma cholesterol, atherosclerosis, and cardiovascular diseases (CVD) reported in the Caucasian populations [12]. The FOXO3 genetic variant rs2802292 (G allele) has been found in higher frequency in centenarians than in younger control participants. This indicates that individuals, who have the G allele, live longer and healthier lives. The FOXO3A gene specifically has been reported to be associated with longevity in Japanese, German, and Italian populations [13]. Throughout this review, a series of other genes involved in longevity will be discussed.

Gene-lifestyle interactions

Healthy aging or longevity is a complex trait and most-likely gene-lifestyle interactions are involved in the process. Today we find more people living longer lives as opposed to the old days when life expectancies were much lower. Could this be due to our population now having genetic variants that promote longevity, the ways we now live our lives, or could both factors in unison make for a healthier aging process allowing us to have greater life expectancies?

A number of genes have been associated with longevity, but we chose to investigate the following three genes, APOE, FOXO3A, and TCF7L2, which have been well studied in different ethnic groups. In humans, APOE e2 allele has been found to be strongly related to longevity in both normal and healthy aging, and FOXO3 has also been found to be consistent to human longevity, but only for some populations [8]. TCF7L2 has been linked together with the Mediterranean diet [14] in longevity. Altogether, we chose to investigate APOE, FOXO3, and TCFL7 for gene-lifestyle interactions regarding aging.

Healthy diet, exercise, and controlling stress levels have also been related to healthy aging with their interactions with genes. These lifestyle components can be executed on a day-to-day basis to increase longevity by repressing cancer-related genes, protecting the human body from frailty, and by promoting positive psychological health. All three components along with epigenomic modifications play crucial roles in setting a strong healthy foundation as the physical and mental body ages. This lifestyle foundation directly correlates with longevity [14]. Our rationale is that a systematic review on updated top longevity-associated genes, lifestyles, and their interactions, specific focus on minority populations in addition to the Caucasian population will help us understand biological and environmental factors (e.g. lifestyle) involved in aging, which are important factors that attribute towards attainment of longevity.

Updated findings of lifestyle, gene and their interactions impacting longevity

The focus of our review includes the involvement of genes, lifestyle choices, and gene-lifestyle interactions as it pertains to longevity and healthy aging. This review paper will also present on the lack of research information concerning minority populations, such as the Hispanic, Asian, and African populations. Inclusion criteria included: (1) keywords of 'lifestyle', 'gene', 'longevity' or 'healthy aging'; (2) English language articles and Human subjects; (3) Seven lifestyle choices of smoking, physical activity, alcohol consumption, healthy diet, body mass index, sleep, and protein Intake; (4) five well documented gene-lifestyle choice interactions were included: APOE and physical activity, TLR-6 and smoking, TCF7L2 and Mediterranean diet, APOA and body mass index, APOE and alcohol consumption and dementia. We first searched for articles through the PubMed with keywords such as 'lifestyle', 'gene', 'longevity' or 'healthy aging' (Figure 1 of workflow). This led to a result of 108 related research articles. We further filtered the results by focusing on English language articles and Human subjects. The research articles were thus narrowed down to 78. Further inquiries were conducted through various combinations of the PubMed searches related to: healthy aging, gene-environment interaction, and individual searches of the genes and lifestyle choices. There were eight genes (TNF, APOE, FOXO3, TOMM40, ACE, APOC1, FOXO1, and IL10), seven lifestyle choices (Smoking, Physical Activity, Alcohol Consumption, Healthy Diet, Body Mass Index, Sleep, and Protein Intake), and five gene-lifestyle choice interactions that were well studied and relevant in our review. The research articles were further analyzed to identify the main findings of lifestyles, polymorphisms, allele frequencies, and sample sizes in four ethnic populations - Caucasian, Asian, African, and Hispanic ethnicities. Exclusion criteria: we excluded non-human studies and non-English Langrage when we used the PubMed Search.

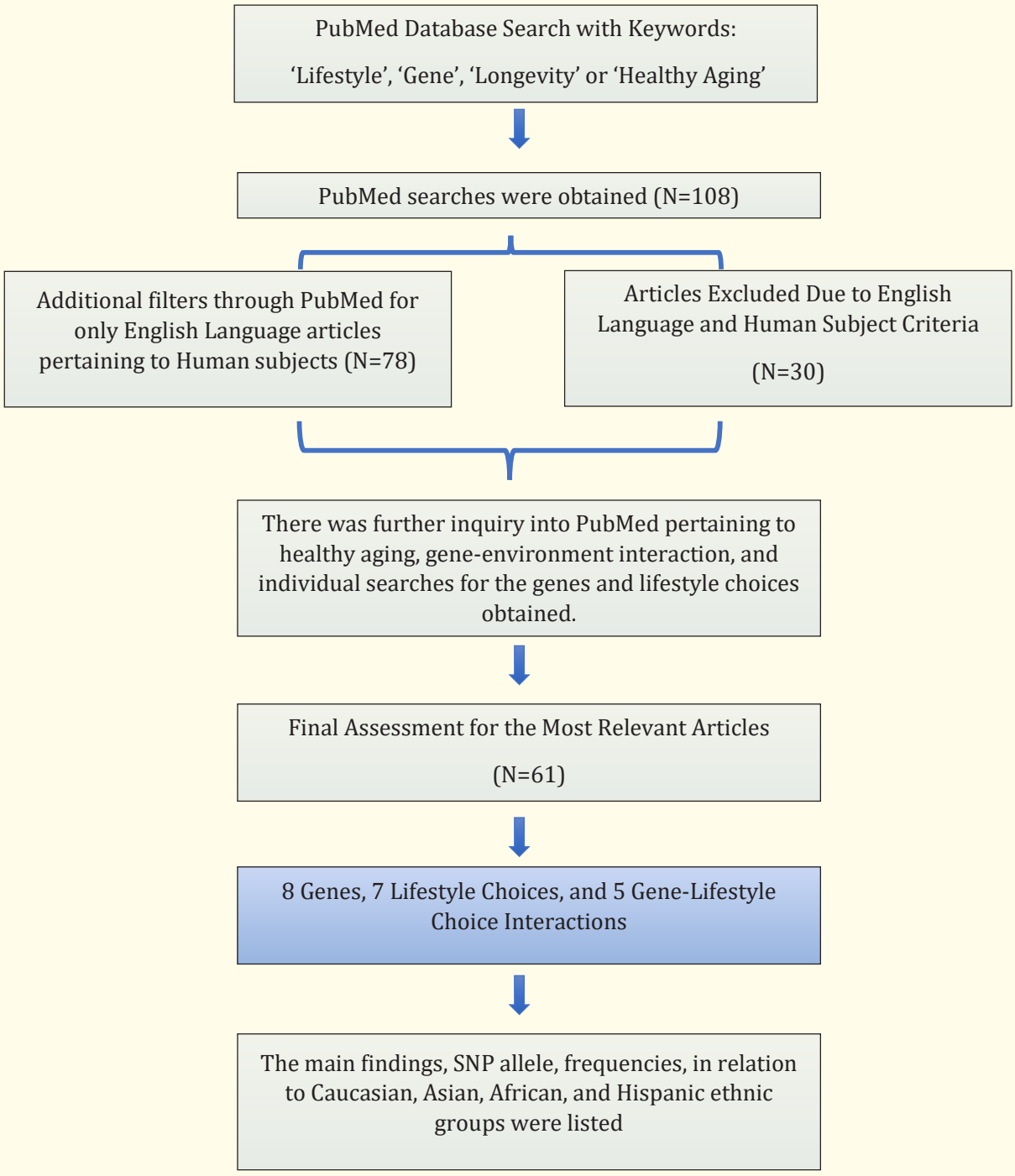

Figure 1*: Workflow of search and selection strategy in a systematic review.*

Study selection process. The figure indicates the study selection process of the systematic literature review.

Lifestyles

Smoking

There are many benefits when it comes to abstaining from smoking. According to our research the benefits also include healthier aging and longevity. A recent study conducted in Sweden that compared the differences in survival based on healthy and unhealthy lifestyle choices found that non-smokers lived on average three years longer than participants who did smoke based on 64,093 participants. Smoking was also shown to be the strongest indicator of mortality and the survival time between participants. There was a difference among all-cause mortality pertaining to men and women. Men had a statistically significant relation to all-cause mortality while the same finding was not discovered for women [9]. Another study conducted in the United States focused on how life extension is affected from quitting smoking in 877,243 subjects. The results found that quitting smoking earlier in life led to the greatest amount of increased life expectancy and the greatest difference was found among participants who quit at age 35 and who continued smoking. Men who quit at age 35 lived 6.9 to 8.5 years longer and women lived 6.1 to 7.7 years longer than other participants who continued to smoke. Even though quitting at an earlier age showed more advantages, there were still benefits to quitting at an older age as well. Men who quit at age 65 lived 1.0 to 2.4 years longer and women lived 2.7 to 3.7 years longer as well [15]. These research papers had large sample sizes, but both focused on majority Caucasian populations. More than ninety percent of the participants in the United States study were Caucasian and the entire Swedish study had Caucasian participants. Information on Asian, Hispanic, and African populations were limited.

Physical activity

Performing any form of physical activity has consistently been linked to living a healthier life. The study conducted in Sweden comparing healthy to unhealthy lifestyle choices also observed the differences that levels of activity have an impact on longevity. Their results showed that men who performed at least 150 minutes of exercise per week lived 0.6 years longer and physically active women lived 1.2 years longer [9]. Another study conducted in China found that physical activity was associated with a 27% decreased risk of mortality as compared to the participants who performed no physical exercise [16]. A recent study found that higher physical activity was significantly associated with lower risk of mortality conducted in 17 different countries (Canada, Sweden, United Arab Emirates, Argentina, Brazil, Chile, Poland, Turkey, Malaysia, South Africa, China, Colombia, Iran, Bangladesh, India, Pakistan, and Zimbabwe). Moderate (150-750 minutes per week) and high (greater than 750 minutes) physical activity was associated with lower risk of mortality regardless of age, sex, or other risk factors [17]. However, the results were not further broken down based on race in each country.

Alcohol consumption

The Swedish study had one section of results in relation to alcohol consumption. According to this study, less than 14 drinks of alcohol per week increased a male's life expectancy by 0.9 years and a woman's by 1.5 years [9]. Another meta-analysis article reports that higher levels of alcohol are associated with mortality while lower doses are inversely proportional to mortality with 2 - 4 drinks for men and 1 - 2 drinks for women per week [18] and study was conducted in the countries of Asian, North American, and European. These findings were also confirmed by a recent combined analysis of lower alcohol assumption (100 g/week, or 5 - 6 standard UK glasses of wine or pints of beer/week) in high-income countries associated with lowest risk of all-cause mortality in 599,912 current drinkers from 83 prospective studies [19]. Thus, people who have lower risk for chronic disorders are expected to increase life expectancy. However, there was no further breakdown based on race, and no specific explanation pertaining to Asian, Hispanic, or African populations.

Healthy diet

A healthy diet has varying characteristics, but all healthy diets have a connection with healthy living and aging. The Swedish study that has been explained before covered the effects of the Dietary Approaches to Stop Hypertension (DASH) diet. The DASH diet involved the consumption of fruits, vegetables, nuts, legumes, fiber-rich foods, whole grains and low-fat dairy products. A DASH diet increased a male's life expectancy by 0.7 years and a female's life expectancy by 0.6 years [9]. There was another study involving the effects of the Nordic diet, which consisted of whole grain bread, oatmeal, apples and pears, root vegetables, cabbage, and shellfish. Participants who consumed the Nordic diet had an 18% lower risk of mortality [20]. The Mediterranean diet was also studied with its longevity association. According to a meta-analysis, there was a consistent relationship among the Mediterranean diet and longevity ranging from

17-31% decrease in mortality [21]. All three articles pertaining to a healthy diet were reported in the Caucasian populations. The meta-analysis focused on five different studies within European and Australian populations. There were three further studies conducted among minority populations. The first study was conducted among the Asian population and found that daily intake of fruits and vegetables was inversely proportional to higher mortality risk while intake of salt-preserved vegetables had a positive association to mortality [16]. The next study monitored the elemental concentrations in the human body of healthy people over the age of 80 in China. It was discovered that four characteristic elements (Cr, Fe, Mn, and Co) were closely related to the healthy elderly people. These elements were found in the drinking water and dietary intake of the healthy elderly people [22]. The second study focused on four diet-quality indexes [the Healthy Eating Index-2010 (HEI-2010), the Alternative HEI-2010 (AHEI-2010), the alternate Mediterranean diet score (aMED), DASH and their reduction in all causes for risk mortality, CVD, and cancer. The study was conducted among a diverse United States population (White, African American, Native Hawaiian, Japanese American, and Latino adults). High HEI-2010, AHEI-2010, aMED, and DASH scores were all inversely associated with risk of all-cause mortality, CVD, and cancer in both men and women [23].

Body mass index

A total of 523 articles with our criteria covered the relationship between body mass index (BMI) and longevity, however we discussed three studies here with large sample sizes. The first article based its data from studies conducted in England, Finland, France, and Sweden, and found that men and women with normal BMI levels lived 7 to 9 years longer without chronic diseases and had healthier wellbeing than obese and overweight participants [24] in 67,490 studied subjects. The other meta-analysis based its information from nineteen different studies and found that all-cause mortality was lowest among the participants with BMIs between 20 and 24.9, and overweight and obese individuals had an increase in all-cause mortality [25] in close to 1.5 million studied participants. A 32-year follow up study was conducted among 113,866 health professionals and found that overweight and obese participants had an increased risk with mortality but adding a healthy lifestyle choice reduced this risk significantly [26]. However, limited information was reported in the Africa, Asian or Hispanic ethnic groups. A study based on a total of 394 Mexican Americans [27] reported that Mexican Americans were at greater risk of mortality than European Americans which might be largely explained ethnic disparity and lower socioeconomic status.

Sleep

The amount of sleep a person has per night significantly affects their life expectancy. According to one study, sleeping at the far ends of the spectrum was associated with increased mortality. Short sleep was considered less than 7 hours and long sleep was greater than 8 hours. Men with short sleep had a 26% increase risk for mortality and women with short sleep had a 21% increase risk for mortality. Men with long sleep had an increased risk of 24% and women had an increased risk of 17% [28] in 21,268 Caucasian participants. Another study conducted in China found that sleep durations less than or equal to 5 hours or greater than or equal to 9 hours had an increased mortality risk as compared to participants that slept 7 hours a day [29] in 113,138 subjects. Therefore, sleeping any more or any less than the average of 7 to 8 hours harms an individual's healthy aging and longevity. Another study was conducted among a Chinese population and found associations between poor sleep quality and higher prevalence of cognitive impairment [30]. No study was found in the Hispanics or Africans with key words of longevity, sleep as of our PubMed search on September 2018.

Protein intake

Participants from one study on protein intake found that consuming a high amount of protein (20% or more of calories from protein) had a 75% increase with mortality between the ages of 50 - 65. Participants from the same study who consumed low amounts of protein (less than 10% of calories from protein) may have optimized health and longevity as well [31] during an 18-year follow-up period. However, subjects over age 65, high protein intake was associated with reduced cancer and overall mortality. The studies subjects consisted of over 85% of 6,381 Caucasian participants followed by 8.7% African Americans and 6.2% Hispanics. Another study on protein intake focused on the differences among plant and animal-based protein. It was discovered that plant protein lowered all-cause and cardiovascular mortality, but when plant protein was replaced by animal protein there was an association with lower mortality as well [32] after adjusting for dietary and lifestyle factors in 131,342 U.S. healthcare professionals including initial and follow-up studies. The authors of this study conclude that protein source is important for long-term health, however, there were limited studies on protein impact on longevity in other minority populations.

Lifestyle	Ethnicity	Sample Size	Main Findings	Notes/Comments	Year
Smoking	Caucasian	n = 64,093	Smoking is a strong predictor for mortality. Men smokers had a significant relation to all-cause mortality, but this was not true for women who smoked	---	(Larsson., *et al*. 2017)
		n = 877,243	Participants who quit smoking earlier on in life had substantial improvement in life extension.	At least 93% of participants were Caucasian	(Taylor., *et al*. 2002)
	Asian	---	---	---	---
	Hispanic	---	---	---	---
	African	---	---	---	---
Physical Activity	Caucasian	n = 64,093	Both male and female participants that exercised had an extension in life	Being physically active meant at least 150 min. per week of exercise	(Larsson., *et al*. 2017)
	Asian	n = 8,959	Those who performed physical activity had about two years longer median survival than those who did not.	---	(Shi., *et al*. 2015)
	Hispanic	---	---	---	---
	African	---	---	---	---
	---	n = 130,843	Participants who performed high physical activity were associated with a reduction in mortality, as compared to participants who performed low physical activity.	Participants were from 17 different countries	(Lear., *et al*. 2017)
Alcohol Consumption	Caucasian	n = 64,093	When alcohol intake was low, life expectancy increased for both genders	Excessive alcohol consumption meant greater than or equal to 14 drinks per week	(Larsson., *et al*. 2017)
	Asian	---	---	---	---
	Hispanic	---	---	---	---
	African	---	---	---	---
	---	n = 1,015,835	Higher levels of alcohol are associated with mortality.	Information based on a Meta-Analysis	(Di Castelnuovo., *et al*. 2006)
Healthy Diet	Caucasian	n = 64,093	A healthy diet increased males and females life expectancy	Healthy Diet meant DASH diet	(Larsson., *et al*. 2017)
		n = 644,961	The healthy diet was associated with a significant lower risk of mortality.	Healthy diet meant Nordic diet.	(Roswall., *et al*. 2015)
		n = 22,918	The healthy diet showed a consistent positive relationship with longevity and decrease in mortality.	Healthy diet meant Mediterranean diet. Information based on a Meta-Analysis.	(Trichopoulou and Critselis 2004)
	Asian	n = 8,959	While fruit and fresh vegetable intake were inversely associated with mortality risk, salt preserved vegetable intake was associated with increased risk of mortality	---	(Shi., *et al*. 2015)
		n = 18	Four elements closely related to the healthy elderly people included Cr, Fe, Mn, and Co. The concentrations of Cr, Fe, Mn, and Co were significantly increased in the longevity group.	---	(Cai., *et al*. 2015a)
	Hispanic	---	---	---	---
	African	---	---	---	---
	---	n = 215,782	In a US multiethnic population, consuming a dietary pattern that achieves a high diet-quality index score is associated with lower risk of mortality from all causes, cardiovascular disease, and cancer in adult men and women	High Diet-Quality Index Score among the Healthy Eating Index-2010, the Alternative HEI-2010, the alternate Mediterranean diet, and the DASH diet	(Harmon., *et al*. 2015)

Body Mass Index	Caucasian	n = 67,490	Obese and overweight participants lived less amount of years with optimal health and an increase in years with chronic diseases.	The findings are based on Meta-Analysis data studies from England, Finland, France, and Sweden	(Stenholm., *et al*. 2017)
		n = 1,460,000	All-cause mortality is the lowest within individuals who have BMI's between 20 and 24.9	Information based on nineteen prospective studies	(Berrington de Gonzalez 2010)
		n = 113,866	Overweight and obese participants are associated with increased risk of mortality	Overweight is a BMI greater than 24.9. Obese means a BMI greater than or equal to 30	(Veronese., *et al*. 2016)
	Asian	---	---	---	---
	Hispanic	---	---	---	---
	African	n = 174,228	BMI increased steadily in all race-sex, education group, specifically consistent higher BMI greater among African women	Black-White disparities in overweight and obesity	(Jackson., *et al*. 2013)
Sleep	Caucasian	n = 21,268	Short amounts of sleep and long amounts of sleep increase mortality for men and women	Short sleep is less than 7 hours. Average sleep is between 7 and 8 hours. Long sleep is more than 8 hours	(Hublin., *et al*. 2007)
	Asian	n = 113,138	Sleep durations less than or more than the average 7 hours a day increased mortality	---	(Cai., *et al*. 2015b)
		n = 660	Subjects with poor sleep quality had significant lower cognitive function scores and higher prevalence of cognitive impairment	---	(Yan 2012)
	Hispanic	---	---	---	---
	African	---	---	---	---
Protein Intake	Caucasian	n = 6,381	High protein intake increased overall mortality. Low protein intake may optimize health span and longevity	Most participants were White (85.1%) followed by Blacks and Hispanics	(Levine., *et al*. 2014)
	Asian	---	---	---	---
	Hispanic	---	---	---	---
	African	---	---	---	---
	---	n = 131,342	Plant protein intake lowers mortality. There was also lowered mortality when plant protein was substituted for animal protein	---	(Song., *et al*. 2016)

Table 1: *Lifestyle choices are associated with health aging.*

Genes

Tumor necrosis factor (TNF) interacts with other gene impact on human longevity

In 2003, a combined analysis of IL-10 and TNF-α genotypes showed that there was a significant increase of the "anti-inflammatory" (IL-10 -1082GG/TNF-α -308GG) genotype in male centenarian as compared with male controls from central and southern Italy (174 centenarian) [33]. There were three studies that involved the rs1800269 polymorphism in the TNF gene that has impact on human longevity. The first two studies focused on the Caucasian populations. The first study found a gene-gene interaction between ADA and TNF-α -308, showing age and sex-specific effects on life-expectancy [11]. The second study found that the survival of allele A carriers of the TNF α-308 GA polymorphism was lower than non-carriers and therefore had detrimental effects on life expectancy, specifically for men [34]. However, among Mestizo Mexican population, a study of 71 elders showed that the elderly female population had an increase in A allele of TNF-308 polymorphism as compared to younger populations and male populations [35], which might be due to small sample size. Future target sequencing of TNF gene in elderly population may provide clearly genetic basis. There was no information on African or Asian populations based on September 2018 PubMed search.

APOE

According to three studies of the APOE, rs429358 polymorphism with comparatively large sample size, participants who lived longer and healthier lives had significantly lower APOE ε 4 alleles [12,36,37]. There was another study that had similar results with centenarians having lower numbers of the APOE ε 4 allele [38]. Several studies with two studies focused on Caucasian populations, one with an Asian population, and one study focused on an African population also supported the findings of lower APOE ε 4 allele frequencies among the oldest elderly populations. A recent replication of Genome Wide Association (GWA) study of ages 85 and 90 in 11,053 postmenopausal White, African American, and Hispanic women from the Women's Health Initiative suggested that APOE alleles are associated with longevity in the White and Hispanic women [39]. Moreover, a recent study of 1067 subjects conducted in Australia also demonstrated that the oldest elderly (95 - 105 years of age) not only had the lowest frequency of APOE ε 4 allele, but also the highest APOE plasma levels compared with individuals aged 56 - 94 [40]. A recent GWA meta-analysis of 606,059 parents' survival also further confirm APOE variants influence longevity in the UK population [41]. In addition of validating previous genomic signals (CDHN2A/B, SH2B3) for longevity, this meta-analysis also discovered two genomic regions associated with longevity, HLA-DQA1/DRB1 and LPA). Moreover, this study also suggests that an increase of one BMI unit can decrease lifespan by 7 months as well as one year of education adds lifespan by 11 months using instrumental variables [41]. The ε4-allele was also confirmed to be negatively associated with exceptional longevity (EL) in three different ethnic cohorts from different countries: Spain (163 EL, age ranged 100 - 111 years old), Italy (79 EL, age ranged 100 - 104 years old), and Japan (729 EL, age ranged 100 - 116 years old) [42].

FOXO3

The rs2802292 polymorphism of the FOXO3 gene is shown to increase life expectancy in individuals who carry the G allele (minor allele). The oldest male participants as compared to younger participants had higher frequencies of rs2802292-G allele, but this was not found in female participants from the Caucasian population [43]. Another study found that females and males with the rs2802292-G allele had 62% - 67% and 61%-73% higher probability of surviving past the age of 100 from the Asian population [44], which confirmed similar findings of the same SNP, where rs2802292-G allele was higher among centenarians than younger control participants in the same population, Asians [13]. Another study on a Chinese population found that different polymorphisms in the FOXO3 gene were associated with longevity in males [45]. A recent study also reported that an association of FDNC5 rs16835198 with human exceptional longevity depends on the presence of the FOXOA3 rs2802292 T-allele in a total of 1565 Japanese subjects (822 middle-aged controls and 743 centenarians) [46]. A resequencing study of the FOXO3 locus and genotyping in three European populations (594 German-, 1264 French-, and 643 Danish elderly, 91-115 years old) confirmed FOXO3 with two SNPs (rs12206094 and rs4946935) associated with longevity. The authors of this study also conducted first functional study and discovered a functional link between FOXO3 common intronic variants and the longevity. However, a recent study showed no association of FOXO3A-rs2802292 with longevity in the White, African American, and Hispanic women aged 85 and 90 in 11,053 postmenopausal subjects [39]. The discrepancies among studies may be due to different study designs, different genotype platforms, diagnosis and subject heterogeneity such as percentages with and without other chronic disorders and/or aged related disorders among elderly subjects.

TOMM40

The SNP, rs2075650 of the TOMM40 gene had an association with survival into old age based on several studies. The first study was conducted among 2073 subjects from a Caucasian population and found that the association with longevity is likely due to linkage disequilibrium between the TOMM40 gene and APOE gene [47]. The second study found that rs2075650is associated with significant survival among Caucasian women up to age 90, but only up to age 85 for Hispanic and African American women [39]. Both studies found that the TOMM40-rs2075650-G allele does have significant association with longevity for the Caucasian, Hispanic, and African populations except Asian.

CHRNA3

A most recent study of European descent found based on 75,244 subjects found a nicotine receptor locus (CHRNA3) was associated with father's survival in old age and this study also confirmed the variants in the TOMM/APOE locus associated with longevity [48]. The CHRNA3 gene was previously associated with smoking and lung cancer. A meta-analysis conducted among 27,848 Caucasian participants found that the APOE/TOMM40 locus had linkage disequilibrium blocks showing association with longevity. They also found that the rs2075650 SNP in APOE/TOMM40 explains about 1.2% of the variance in the longevity phenotype [49] and confirmed by two studies by Joshi., *et al.*: a locus near CHRNA3/5 differentially affecting paternal lifespan (effect -0.86 years per allele [50] and a GWA meta-analysis of 606,059 parents on this gene in the UK population [41].

ACE

A total of 70 studies based on key words of longevity and ACE gene were found from a PubMed search on September 2018. Among which, the three studies on the rs1799752 polymorphism of the ACE gene showed consistent results of the association between the D allele (Alu Deletion) of rs1799752 and centenarians from European descent, where the oldest aged groups (centenarians) had significantly higher frequencies of the D allele as compared to younger controlled participants [51,52]. In the Chinese population, it was found that the Uighur longevity group in Hotan (aged 90-113 years) had significantly higher frequency of the D allele as compared to the Uighur older group in Hotan (aged 59 - 70 years) [53]. According to a meta-analysis that consisted of 12,288 Asian and Caucasian participants, there is a modest significant positive association between the ACE-D allele and exceptional longevity [54]. The studies we found had information from Caucasian and Asian groups, but none for Hispanic or African groups. Moreover, there are also inconsistent findings ACE genetic variants in association with longevity with other some studies.

APOC1

The rs4420638 polymorphism of the APOC1 gene is significantly associated with longevity. Two meta-analysis articles conducted in European descent populations found that rs4420638at the TOMM40/APOE/APOC1 gene locus showed significant association with longevity [55,56]. Based on the database of the dbSNP search (https://www.ncbi.nlm.nih.gov/snp/rs4420638), this SNP, rs4420638, is located at 3'UTR of the APOC1 gene, however, TOMM40 and APOE genes are located at the 5'UTR of APOC1 gene, indicating three genes are located close to one another on the same chromosome of 19q13.32. Another study that also found that the rs4420638-G allele polymorphism was associated with longevity and healthy aging in the White women. However, this association was not observed in the Asian, Hispanic, or African populations [39]. Therefore, all the results were relevant towards Caucasian populations, and more studies are needed for other minorities, such as Asian, Hispanic, or African populations.

FOXO1

The SNP, rs2755209-A allele of the FOXO1 gene is inversely associated with longevity. According to two studies, there is reduced allele frequency of rs2755209-A allele in nonagenarians and centenarians compared to younger controlled participants [13,57] in the population from the Netherlands. These findings were also confirmed by Dr. Zeng., *et al.* 2016 in two independent cohorts from Chinese populations, where the authors also found that interactions of FOXO1 rs2755209-A allele and tea-compounds on the assumption of tea drinking inhibiting FOXO1 gene expression and its biological functions, that reduces the negative impacts of FOXO1 rs2755209-A allele on longevity [58]. There was no information found on Hispanic or African populations. A recent review summarized that molecular and clinical features of FOXO transcription factor. Increasing evidence demonstrates that FOXO family consists of FOXO1, 3, 4 and 6, which play important roles in maintaining optimum body function and homeostasis. However if these mechanisms dysregulate it will result in the development of age-related diseases [59].

Gene	Polymorphism	Ethnicity	Frequency*	Sample Size	Associated with Phenotypes (Longevity)	Notes/ Comments	Year
TNF	rs1800629 (G Major Allele; A Minor Allele)	Caucasian	0.167	n = 1071	There were significant loci interactions for males between the TNF-a 308 polymorphism and ADA 22G>A polymorphism in which there was an increase in life expectancy. The allele A carriers decreased with age and had a negative association with longevity among the Italian population	rs1800629 is TNF-a (308G>A) rs73598374 is ADA (22G>A)	(Napolioni., et al. 2011)
				n = 747			(Cardelli., et al. 2008)
		Asian	0.02	---			---
		African	0.12	---			---
APOE	rs429358 (T Major Allele; C Minor Allele)	Caucasian	0.15	n = 391	The APOE ε4 allele is significantly lower in participants who lived long and healthy lives in Caucasian and Asian populations Centenarians had significantly depleted rsr429358 in the African American population as well. APOE is significantly associated with survival up to age 90 for White and Hispanic women association meta-analysis of 606,059 parents' survival	If the rs429358 allele is (C) and the same chromosome harbors the rs7412(C) allele, the combination is known as an APOE-ε4 allele	(Stakias., *et al*. 2006; Ryu., *et al*. 2016; Jian-Gang., *et al*. 1998) (Muenchhoff 2017).
				n = 950			
				n = 1067]			
				n = 8,656			
		UK Caucasian		N = 606,059 parents' survival			(Joshi., *et al*. 2017)
		Asian	0.01	n = 236			(Jian-Gang., *et al*. 1998)
		Hispanic	0.0859	n =539			(Shadyab., *et al*. 2017)
		African	0.27	n = 1519			(Jazwinski., *et al*. 2010)
FOXO3	rs2802292 (T Major Allele; G Minor Allele)	Caucasian	0.43	n = 1,825	Significant G allelic frequency differences between oldest and youngest male participants. Women and men who carry the minor allele, G, had a higher probability of surviving past the age of 100. The G allele was higher among centenarians. FOXO3 gene polymorphisms are associated with longevity in males	---	(Soerensen., *et al*. 2010)
		Asian	0.31	n = 1,820			(Zeng., *et al*. 2010)
				n = 1,817			(Li., *et al*. 2009)
				n = 1462			(Lin., *et al*. 2016)
		Hispanic	0.4063	---			---
		African	0.17	---			---
TOMM40	rs2075650 (A Major Allele; G Minor Allele)	Caucasian	0.13	n = 2,073	The G allele of the polymorphism was associated with survival into old age at the genome-wide significance level. G allele specifically linked to longevity into old age for Caucasian, Hispanic, and African populations, but no data on Asian populations was presented. The APOE/TOMM40 locus showed association with longevity	Information is based on two meta-analysis research papers	(Deelen., *et al*. 2011)
				n = 8,656			(Shadyab., *et al*. 2017)
				n = 27,848			(Fortney., *et al*. 2015)
		Asian	0.097	---			---
		Hispanic	0.0962	n = 539			(Shadyab., *et al*. 2017)
		African	0.13	n = 1,858			(Shadyab., *et al*. 2017)
ACE	rs1799752 (Alu Insertion/ Deletion)	Caucasian	0	n = 1710	There was a significant association between the Alu deletion allele and centenarians in Caucasian and Asian populations	Alu Insertion (I) and Deletion (D) have no allelic frequencies. Information based on a meta-analysis study consisting of Caucasian and Asian subjects	(Seripa., *et al*. 2006)
				n = 394			(Faure-Delanef., *et al*. 1998)
		Asian	0	n = 424			(Rahmutula., *et al*. 2002)
		Hispanic	0	---			---
		African	0	---			---
		---	0	n = 12,288			(Garatachea., *et al*. 2013)
APOC1	rs4420638 (A Major Allele; G Minor Allele)	Caucasian	0.186	n = 2,118	The SNP at the TOMM40/APOE/APOC1 gene locus showed association with longevity. Caucasian women with the G allele were associated with longevity and healthy aging	Meta-Analysis Research Paper	(Beekman., *et al*. 2013; Deelen., *et al*. 2014)
				n = 7,729			
				n = 8,656			(Shadyab., *et al*. 2017)
		Asian	0.08	---			---
		Hispanic	0.0938	n = 539			(Shadyab., *et al*. 2017)
		African	0.15	n = 1,858			(Shadyab., *et al*. 2017)
FOXO1	rs2755209 (C Major Allele; A Minor Allele)	Caucasian	0.418	n = 745	Single gene analysis showed that FOXO1 is expressed at lower levels among nonagenarians. An allele was lower in centenarian groups as compared to controls	---	(Passtoors., *et al*. 2013)
		Asian	0.337	n = 1,817			(Li., *et al*. 2009)
		Hispanic	0.5	---			---
		African	0.384	---			---

Table 2: *Genes/variants are in association with health aging.*

IL10

The rs1800896 polymorphism of the IL10 gene is significantly associated with longevity among men. There were two studies conducted among the Caucasian populations that consistently found a relationship among high frequencies of the rs1800896-G allele with centenarians as compared to younger controlled participants [33,60]. Another study conducted in a Asian population found that the 1082 polymorphism-G allele in the promoter region of the IL-10 was significantly associated with longevity in men ($P < 0.05$) but not in women ($P < 0.05$) [61]. There was no information found for Hispanic or African populations.

Gene-lifestyle interactions

APOE and physical activity

One of the most well-known genes to be linked with both healthy longevity and simply aging in general is APOE. As we also know, a moderate amount of physical activity is essential in living a long healthy life. In a study, 3,375 Caucasian participants were monitored and examined over time to see who developed dementia and who did not. There was a significant correlation in the participants, who developed dementia and were more likely to carry the APOE ε4 allele along with having done less physical activities [62]. In another study, 18 sedentary obese men were monitored in blood pressure (BP) while exercise training. It was found that individuals with APOE ε4 allele along with exercise training showed a significant decrease in systolic BP as opposed to individuals with APOE ε2 allele. This would also suggest that individuals with APOE ε4 allele are more at high risk for CVD, leading to mortality [63]. Male subjects with an APOE ε4 allele who participated in < an hour physical activity/day and had an increased risk of cognitive decline in 347 elderly Dutch men, mean age of the subjects, 74.6 ± 4.3 years [64].

TLR-6 and smoking

T-cell receptors are important proteins in the innate response of our immune system. In the first study, a total of 1,544 individuals were recruited from the Poland population to investigate whether non-smokers could be protected from age-related diseases. It was found that non-smoking elderly subjects with the TLR-6 polymorphism, rs5743810 - T allele (C→T, P249S) is associated with healthy aging possibly by decreased sensitivity of the innate immune response in the Eastern European Caucasians [65]. Future study is needed to confirm the findings.

TCF7L2 and Mediterranean diet

The TCF7L2 gene and the Mediterranean diet interaction is one of the most well-known gene-diet interactions. A strict Mediterranean diet can influence the effects of the rs7903146-T allele of TCF7L2 gene, which is normally responsible for increasing the risk for diabetes. A beneficial effect of the Mediterranean diet is observed only in subjects who carried rs7903146-1 or 2 T alleles. In the Belfast Elderly Longitudinal Free-living Ageing Study (BELFAST) study, which was the first study, 90-year-old subjects were recruited through their general practitioners. These nonagenarians identified five important insights in their long lives, including genes, diet, good health, physical activity, social networks and resilience. The authors of the BELFAST study and another study [66] concluded an interaction between the TCF7L2 variants and Mediterranean Diet. The second study used a total of 1,349 individuals from Northern/Central Italy, and in combination with the BELFAST study reported a reduced frequency of the diabetes-related rs7903146- T allele of TCF7L2 gene in the super centenarian subjects, but an enrichment of the CC genotype. This suggests that the CC genotype play a protective role in Italian centenarians exposed to a Mediterranean diet [8,66]. The third study used a total of 235 participants without diabetes from the Leiden Longevity Study. This study found that rs7903146-T allele carriers of the TCF7L2 gene were associated with a higher mean 24-hour glucose level than CC carriers [67].

APOA and body mass index

Results pertaining to gene-diet interaction between APOA and BMI in three studies, the Framingham Offspring Study [68], the Genetics of Lipid Lowering Drugs and Diet Network Study [69] and Boston-Puerto Rican Centers on Population Health and Health Disparities Study [70]. The first two studies had Caucasian populations, the third study was conducted in the US Hispanic population. When saturated fat intake was low, the subjects carried rs5082-C allele (-265T>C) of the APOA2 gene did not affect BMI. However, when saturated fat intake

was high, this genetic variant is strongly associated with BMI and obesity. Therefore, the effect of saturated fat on BMI and obesity is highly dependent on the subjects with APOA2 - rs5082-C allele [71]. This association was also confirmed in Mediterranean and Asian populations where the CC genotype of rs5082 was also significantly associated with higher obesity prevalence, with a high-saturated fat intake [72]. No information was reported in the African population.

APOE and alcohol consumption and dementia

Two different studies show similar results pertaining to the APOE gene and alcohol consumption relationship [73,74]. The first study included 610 participants and found that those with one or more APOE ε4 alleles showed greater decline in learning and memory in comparison with those who did not have any APOE ε4 alleles. This study also found that moderate alcohol consumption was associated with greater decline in learning and memory in participants who had the APOE ε4 allele. However, those who did not have the APOE ε4 allele and had moderate alcohol consumption were associated with an increase in learning and memory. The same trend was observed in participants who were light alcohol consumers with and without APOE ε4 allele. This study showed that the relationship between late life alcohol consumption and the decline in learning and memory is modified according to the presence or absence of the APOE ε4 allele [73]. The second study consisted of 1,018 participants from two areas in eastern Finland and found that compared with participants who never drank and did not have the APOE ε4 allele present, participants who had the APOE ε4 allele and drank infrequently were 2.3 times more likely to develop dementia, and participants who drank frequently and had the APOE ε4 allele present were 3.6 times more likely to develop dementia. This study showed that the presence or absence of the APOE ε4 gene in combination with alcohol consumption has a major effect, as risk of dementia increases with midlife alcohol consumption specifically among participants who had the APOE ε4 allele present [74]. The similar findings were also observed in 580 unrelated South African subjects [75]. A SNP rs769450 in the APOE gene also showed interactions between alcohol drinking and physical activity, and triglyceride (TG) levels in 1193 Korean men [76]. A future study on APOE genetic variants and alcohol consumption is needed for other minority populations, such as Hispanic population.

Gene	Lifestyle	Ethnicity	Sample Size	Outcome	Year
APOE	Physical Activity	Caucasian	n = 3375	An inverse association was found for patients with APOE ε4 carriers and physical activity	(Podewils*., et al.* 2005) (Hagberg*., et al.* 1999)
		Asian	---	---	
		Hispanic	---	---	
		African	---	---	
		---	n = 18	Low number of physical activities along with having the APOE ε4 allele was associated with higher relative risk of cardiovascular disease	
TLR-6	Smoking	Caucasian	n = 1544	Non-smoking elderly subjects with the S (minor) allele is associated with healthy aging	(Hamann*., et al.* 2016)
		Asian	---	---	
		Hispanic	---	---	
		African	---	---	

TCF7L2	Mediterranean Diet	Caucasian	n = 1349	There was a reduced frequency of the diabetes-related rs7903146 T allele of TCF7L2 in the centenarians, but a higher frequency of the CC genotype. This suggests that the CC genotype could be a protective variant in Italian centenarians exposed to a Mediterranean diet	(Rea., *et al.* 2015; Garagnani., *et al.* 2013) (van der Kroef., *et al.* 2016)
			n = 235	This study showed that T allele carriers of the TCF7L2 gene were associated with a higher mean 24-hour glucose level than C allele carriers	
		Asian	---	---	
		Hispanic	---	---	
		African	---	---	
APOA2	Body Mass Index	Caucasian	n = 1454	A meta-analysis found a relationship between gene-diet interaction and BMI, participants with the APOA2, rs5082-CC genotype showed susceptible to increased BMI and obesity when consuming a high saturated fat diet	(Corella., *et al.* 2009) (Feinleib., *et al.* 1975) (Corella., *et al.* 2007) (Lai., *et al.* 2008) (Corella., *et al.* 2011)
			n = 1078		
		Asian	n = 4602		
			n = 3605		
		Hispanic	n = 930		
		African	---		
APOE	Alcohol Consumption	Caucasian	n = 610	Moderate alcohol consumption during late life was associated with an increase in learning and memory in subjects without APOE e4 allele, whereas decline among subjects with APOE ε4 allele	(Downer., *et al.* 2014) (Anttila., *et al.* 2004) (Son., *et al.* 2015) (Luckhoff., *et al.* 2016)
			n = 1018	In comparison with participants who neither drink nor have the APOE e4 allele, those who drank infrequently were 2.3 times more likely to develop dementia, and those who drank frequently and had the APOE e4 allele were 3.6 times more likely develop dementia	
		Asian	n = 1193	APOE polymorphism rs769450 showed interactions between alcohol and physical activity among Korean men	
		Hispanic	---	---	
		African	n = 580	APOE genotype modified the association between alcohol intake and total cholesterol in study participants with a positive family history of Alzheimer's disease (p = 0.026), with a significant positive association between these parameters being limited to ε4 allele carriers	

Table 3: *Interaction of lifestyles and genes impacts on health aging.*

Discussion

Longevity and healthy aging are elements that people strive to attain as they become older. Our review focused on the importance of lifestyle choices, genetic composition, and their interactions. Based on the results of current findings, our review has concluded that lifestyle choices, genetic variants, and the interaction between the two are related to the length of a person's lifespan as well as how healthy the person ages. Those studies were reported mainly in the Caucasian population. Very limited studies were observed in other minorities, such as Hispanic, Asian, and African populations, although there were some studies, but sample size was small or moderate. The healthy lifestyle choices a person makes consistently showed an increase in life expectancy and decrease in mortality regardless of ethnicity, such as whether they abstained from smoke, healthy diet, or physical activity throughout their lives. However, there are also ethnically specific genetic variants and lifestyles which may benefit in healthy aging. In contrast, unhealthy lifestyle choices such as abnormal sleeping and high BMI were associated with an increase in mortality and decrease in longevity. The genetic profile of a person carries was also found to be a relevant aspect based on our reviewing of scientific literature. The genetic variants we reviewed showed significant associations with longevity. However, there were differences of allele frequencies of the longevity associated polymorphisms based on specific populations contributed to. Most of chronic diseases (e.g. diabetes, hypertension) associated variants were observed less common among people with longevity and healthy aging. Our findings on gene-lifestyle interactions present a review of the relationships between genetic variants and certain lifestyle choices. The results align with what we expected to find - that genes, lifestyle choices and their interactions are involved in longevity and healthy aging.

Conclusion

An important component of our review involved trying to find relevant articles that presented data on genes, and gene-environment interactions and healthy aging or longevity in minority populations in addition to the Caucasian population. Evidence was discovered consistently about correlations of healthy aging and longevity with lifestyle choices, genes, and gene-lifestyle interactions reported in mainly Caucasian populations. From our systemically literature review, we found that there was evidence of ethnic specific polymorphisms, lifestyles, and their interactions which influence longevity and healthy aging. Some findings were not the same across different populations. Some genetic variants or lifestyles may benefit healthy aging in one population but have risk or no association for other ethnic groups. Therefore, future studies are required focusing on minority populations with large sample sizes and replication/confirmation findings. It is critical to address the gaps in gene, gene-environment interactions and longevity and healthy aging in diverse ethnic populations.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

Yes, data will be shared, because all authors agreed.

Competing Interests

All authors have reported no financial interests or potential conflicts of interest.

Funding

None declared, however, we acknowledge the UTRGV faculty start up fund for Dr. Chun Xu.

Authors' Contributions

BBS, AV were involved in literature search, prepared manuscript, critically revised manuscript. drafted the paper. Both made equal contribution to the paper as 1st authors; SH, LP, SL, MZ also made signification to the manuscript preparation (such as all sections of

the paper, tables) and drafted the paper; MZ, KSW, SN revised the manuscript and provided critical comments and suggestions; CX, as corresponding author, supervised the entire study and revised the manuscript before submission. All authors have read and agreed with the final version of this manuscript.

Acknowledgements

We acknowledged Lizette Padilla for her contribution to this review paper.

Bibliography

1. Rodriguez-Rodero S., *et al*. "Aging genetics and aging". *Aging and Disease* 2.3 (2011): 186-195.
2. Stefánsson H. "The science of ageing and anti-ageing". *EMBO Reports* 6.1 (2005): S1-S3.
3. "National Center for Health and Statistics". Life Expectancy (2017).
4. Arias E., *et al*. "National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics". *National Vital Statistics System* 66.3 (2017): 1.
5. Gamble S., *et al.* "Surveillance for Certain Health Behaviors and Conditions Among States and Selected Local Areas - Behavioral Risk Factor Surveillance System, United States, 2013 and 2014". *MMWR Surveillance Summaries* 66.16 (2017): 1-144.
6. Ostan R., *et al.* "Gender, aging and longevity in humans: an update of an intriguing/neglected scenario paving the way to a gender-specific medicine". *Clinical Science* 130.19 (2016): 1711-1725.
7. Passarino G., *et al.* "Human longevity: Genetics or Lifestyle? It takes two to tango". *Immunity and Ageing* 13 (2016): 12.
8. Rea JN., *et al.* "Genes and life-style factors in BELFAST nonagenarians: Nature, Nurture and Narrative". *Biogerontology* 16.5 (2015): 587-597.
9. Larsson SC., *et al.* "Combined impact of healthy lifestyle factors on lifespan: two prospective cohorts". *Journal of Internal Medicine* 282.3 (2017): 209-219.
10. Sebastiani P., *et al.* "Genetic signatures of exceptional longevity in humans". *PLoS One* 7.1 (2012): e29848.
11. Napolioni V., *et al.* "Age- and gender-specific epistasis between ADA and TNF-alpha influences human life-expectancy". *Cytokine* 56.2 (2011): 481-488.
12. Stakias N., *et al.* "Lower prevalence of epsilon 4 allele of apolipoprotein E gene in healthy, longer-lived individuals of Hellenic origin". *Journals of Gerontology Series A: Biological Sciences and Medical Science* 61.12 (2006): 1228-1231.
13. Li Y., *et al*. "Genetic association of FOXO1A and FOXO3A with longevity trait in Han Chinese populations". *Human Molecular Genetics* 18.24 (2009): 4897-904.
14. Rea IM., *et al.* "Living long and ageing well: is epigenomics the missing link between nature and nurture?". *Biogerontology* 17.1 (2016): 33-54.
15. Taylor DH., *et al.* "Benefits of smoking cessation for longevity". *American Journal of Public Health* 92.6 (2002): 990-996.

16. Shi Z., *et al.* "Food Habits, Lifestyle Factors and Mortality among Oldest Old Chinese: The Chinese Longitudinal Healthy Longevity Survey (CLHLS)". *Nutrients* 7.9 (2015): 7562-7579.

17. Lear SA., *et al.* "The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study". *Lancet* 390.10113 (2017): 2643-2654.

18. Di Castelnuovo A., *et al.* "Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies". *JAMA Internal Medicine*166.22 (2006): 2437-4245.

19. Wood AM., *et al.* "Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies". *Lancet* 391.10129 (2018): 1513-1523.

20. Roswall N., *et al.* "Adherence to the healthy Nordic food index and total and cause-specific mortality among Swedish women". *European Journal of Epidemiology* 30.6 (2015): 509-517.

21. Trichopoulou A and Critselis E. "Mediterranean diet and longevity". *European Journal of Cancer Prevention* 13.5 (2004): 453-456.

22. Cai D., *et al*. "A correlation between diet and longevity characterization by means of element profiles in healthy people over 80 years from a Chinese longevous region". *Biological Trace Element Research* 165.1 (2015): 18-29.

23. Harmon BE., *et al.* "Associations of key diet-quality indexes with mortality in the Multiethnic Cohort: the Dietary Patterns Methods Project". *American Journal of Clinical Nutrition* 101.3 (2015): 587-597.

24. Stenholm S., *et al.* "Body mass index as a predictor of healthy and disease-free life expectancy between ages 50 and 75: a multicohort study". *International Journal of Obesity* 41.5 (2017): 769-775.

25. Berrington de Gonzalez A., *et al.* "Body-mass index and mortality among 1.46 million white adults". *New England Journal of Medicine* 363.4 (2010): 529-536.

26. Veronese N., *et al.* "Combined associations of body weight and lifestyle factors with all cause and cause specific mortality in men and women: prospective cohort study". *British Medical Journal* 355 (2016): i5855.

27. Espinoza SE., *et al*. "The Hispanic paradox and predictors of mortality in an aging biethnic cohort of Mexican Americans and European Americans: the san antonio longitudinal study of aging". *Journal of the American Geriatrics Society* 61.9 (2013): 1522-1529.

28. Hublin C., *et al.* "Sleep and mortality: a population-based 22-year follow-up study". *Sleep* 2007 30.10: 1245-1253.

29. Cai H., *et al.* "Sleep duration and mortality: a prospective study of 113 138 middle-aged and elderly Chinese men and women". *Sleep* 38.4 (2015): 529-536.

30. Yan HC-QDB-RZ. "Association Between Sleep Quality and Cognitive Impairment Among Chinese Nonagenarians/Centenarians". *Journal of Clinical Neurophysiology* 29.3 (2012): 250-255.

31. Levine ME., *et al*. "Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population". *Cell Metabolism* 19.3 (2014): 407-417.

32. Song M., *et al.* "Association of Animal and Plant Protein Intake With All-Cause and Cause-Specific Mortality". *JAMA Internal Medicine* 176.10 (2016): 1453-1463.

33. Lio D., *et al*. "Inflammation, genetics, and longevity: further studies on the protective effects in men of IL-10 -1082 promoter SNP and its interaction with TNF-alpha -308 promoter SNP". Journal of Medical Genetics 40.4 (2003): 296-299.

34. Cardelli M., *et al.* "A genetic-demographic approach reveals male-specific association between survival and tumor necrosis factor (A/G)-308 polymorphism". *Journals of Gerontology Series A: Biological Sciences and Medical Science* 63.5 (2008): 454-460.

35. Soto-Vega E., *et al.* "Human leukocyte antigen class I, class II, and tumor necrosis factor-alpha polymorphisms in a healthy elder Mexican Mestizo population". *Immunity and Ageing* 2 (2005): 13.

36. Ryu S., *et al.* "Genetic landscape of APOE in human longevity revealed by high-throughput sequencing". *Mechanisms of Ageing and Development* 155 (2016): 7-9.

37. Jian-Gang Z., *et al.* "Apolipoprotein E and longevity among Han Chinese population". *Mechanisms of Ageing and Development* 104.2 (1998): 159-167.

38. Jazwinski SM., *et al.* "HRAS1 and LASS1 with APOE are associated with human longevity and healthy aging". *Aging Cell* 9.5 (2010): 698-708.

39. Shadyab AH., *et al.* "Replication of Genome-Wide Association Study Findings of Longevity in White, African American, and Hispanic Women: The Women's Health Initiative". *Journals of Gerontology Series A: Biological Sciences and Medical Science* 72.10 (2017): 1401-1406.

40. Muenchhoff J., *et al.* "Plasma apolipoproteins and physical and cognitive health in very old individuals". *Neurobiology* 55 (2017): 49-60.

41. Joshi PK., *et al.* "Genome-wide meta-analysis associates HLA-DQA1/DRB1 and LPA and lifestyle factors with human longevity". *Nature Communications* 8.1 (2017): 910.

42. Garatachea N., *et al*. "ApoE gene and exceptional longevity: Insights from three independent cohorts". *Experimental Gerontology* 53 (2014): 16-23.

43. Soerensen M., *et al.* "Replication of an association of variation in the FOXO3A gene with human longevity using both case-control and longitudinal data". *Aging Cell* 9.6 (2010): 1010-1017.

44. Zeng Y., *et al.* "Effects of FOXO genotypes on longevity: a biodemographic analysis". *Journals of Gerontology Series A: Biological Sciences and Medical Science* 65.12 (2010): 1285-1299.

45. Lin R., *et al.* "Genetic Association Analysis of Common Variants in FOXO3 Related to Longevity in a Chinese Population". *PLoS One* 11.12 (2016): e0167918.

46. Fuku N., *et al.* "Epistasis, physical capacity-related genes and exceptional longevity: FNDC5 gene interactions with candidate genes FOXOA3 and APOE". *BMC Genomics* 18.8 (2017): 803.

47. Deelen J., *et al.* "Genome-wide association study identifies a single major locus contributing to survival into old age the APOE locus revisited". *Aging Cell* 10.4 (2011): 686-698.

48. Pilling LC., *et al.* "Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants". *Aging (Albany NY)* 8.3 (2016): 547-560.

49. Fortney K., *et al.* "Genome-Wide Scan Informed by Age-Related Disease Identifies Loci for Exceptional Human Longevity". *PLoS Genetics* 11.12 (2015): e1005728.

50. Joshi PK., *et al.* "Variants near CHRNA3/5 and APOE have age- and sex-related effects on human lifespan". *Nature Communications* 7 (2016): 11174.

51. Seripa D., *et al*. "Sex differences in the association of apolipoprotein E and angiotensin-converting enzyme gene polymorphisms with healthy aging and longevity: a population-based study from Southern Italy". *Journals of Gerontology Series A: Biological Sciences and Medical Science* 61.9 (2006): 918-923.

52. Faure-Delanef L., *et al*. "Plasma concentration, kinetic constants, and gene polymorphism of angiotensin I-converting enzyme in centenarians". *Clinical Chemistry* 44.10 (1998): 2083-2087.

53. Rahmutula D., *et al.* "Angiotensin-converting enzyme gene and longevity in the Xin Jiang Uighur autonomous region of China: an association study". *Journals of Gerontology Series A: Biological Sciences and Medical Science* 57.1 (2002): M57-60.

54. Garatachea N., *et al*. "The ACE DD genotype and D-allele are associated with exceptional longevity: a meta-analysis". *Ageing Research Reviews* 12.4 (2013): 1079-1087.

55. Beekman M., *et al.* "Genome-wide linkage analysis for human longevity: Genetics of Healthy Aging Study". *Aging Cell* 12.2 (2013): 184-193.

56. Deelen J., *et al.* "Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age". *Human Molecular Genetics* 23.16 (2014): 4420-4432.

57. Passtoors WM., *et al*. "Gene expression analysis of mTOR pathway: association with human longevity". *Aging Cell* 12.1 (2013): 24-31.

58. Zeng Y., *et al.* "Interaction Between the FOXO1A-209 Genotype and Tea Drinking Is Significantly Associated with Reduced Mortality at Advanced Ages". *Rejuvenation Research* 19.3 (2016): 195-203.

59. Tia N., *et al.* "Role of Forkhead Box O (FOXO) transcription factor in aging and diseases". *Gene* 648 (2018): 97-105.

60. Lio D., *et al.* "Gender-specific association between -1082 IL-10 promoter polymorphism and longevity". *Genes and Immunity* 3.1 (2002): 30-33.

61. Khabour OF and Barnawi JM. "Association of longevity with IL-10 -1082 G/A and TNF-alpha-308 G/A polymorphisms". *International Journal of Immunogenetics* 37.4 (2010): 293-298.

62. Podewils LJ., *et al.* "Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study". *American Journal of Epidemiology* 161.7 (2005): 639-651.

63. Hagberg JM., *et al.* "Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent". *Hypertension* 34.1 (1999): 18-23.

64. Schuit AJ., *et al*. "Physical activity and cognitive decline, the role of the apolipoprotein e4 allele". *Medicine and Science in Sports and Exercise* 33.5 (2001): 772-777.

65. Hamann L., *et al*. "TLR-6 SNP P249S is associated with healthy aging in nonsmoking Eastern European Caucasians - A cohort study". *Immunity and Ageing* 13 (2016): 7.

66. Garagnani P., *et al.* "Centenarians as super-controls to assess the biological relevance of genetic risk factors for common age-related diseases: a proof of principle on type 2 diabetes". *Aging (Albany NY)* 5.5 (2013): 373-385.

67. van der Kroef S., *et al.* "Association between the rs7903146 Polymorphism in the TCF7L2 Gene and Parameters Derived with Continuous Glucose Monitoring in Individuals without Diabetes". *PLoS One* 11.2 (2016): e0149992.

68. Feinleib M., *et al*. "The Framingham Offspring Study. Design and preliminary data". *Preventive Medicine* 4.4 (1975): 518-25.

69. Corella D., *et al*. "The -256T>C polymorphism in the apolipoprotein A-II gene promoter is associated with body mass index and food intake in the genetics of lipid lowering drugs and diet network study". *Clinical Chemistry* 53.6 (2007): 1144-1152.

70. Lai CQ., *et al*. "PPARGC1A variation associated with DNA damage, diabetes, and cardiovascular diseases: the Boston Puerto Rican Health Study". *Diabetes* 57.4 (2008): 809-816.

71. Corella D., *et al.* "APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations". *Archives of Internal Medicine* 169.20 (2009): 1897-1906.

72. Corella D., *et al.* "Association between the APOA2 promoter polymorphism and body weight in Mediterranean and Asian populations: replication of a gene-saturated fat interaction". *International Journal of Obesity* 35.5 (2011): 666-675.

73. Downer B., *et al.* "The relationship between midlife and late life alcohol consumption, APOE e4 and the decline in learning and memory among older adults". *Alcohol Alcohol* 49.1 (2014): 17-22.

74. Anttila T., *et al*. "Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population-based study". *BMJ* 329.7465 (2004): 539.

75. Luckhoff HK., *et al.* "Apolipoprotein E genotyping and questionnaire-based assessment of lifestyle risk factors in dyslipidemic patients with a family history of Alzheimer's disease: test development for clinical application". *Metabolic Brain Disease* 31.1 (2016): 213-224.

76. Son KY., *et al.* "Genetic association of APOA5 and APOE with metabolic syndrome and their interaction with health-related behavior in Korean men". 14 (2015): 105.

Volume 11 Issue 7 July 2019