JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 2, 2021

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

*JACC* STATE-OF-THE-ART REVIEW

# Cardiovascular Aging and Longevity

## *JACC* State-of-the-Art Review

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**ABSTRACT**

Cardiovascular aging and longevity are interrelated through many pathophysiological mechanisms. Many factors that promote atherosclerotic cardiovascular disease are also implicated in the aging process and vice versa. Indeed, cardiometabolic disorders such as hyperglycemia, insulin resistance, dyslipidemia, and arterial hypertension share common pathophysiological mechanisms with aging and longevity. Moreover, genetic modulators of longevity have a significant impact on cardiovascular aging. The current knowledge of genetic, molecular, and biochemical pathways of aging may serve as a substrate to introduce interventions that might delay cardiovascular aging, thus approaching the goal of longevity. In the present review, the authors describe pathophysiological links between cardiovascular aging and longevity and translate these mechanisms into clinical data by reporting genetic, dietary, and environmental characteristics from long-living populations. (J Am Coll Cardiol 2021;77:189–204) © 2021 by the American College of Cardiology Foundation.

Scientific research on mechanisms of aging and means of achieving longevity has provided a considerable body of knowledge during the past decades, which is constantly growing. Five places in the world, including Ikaria island in Greece, often termed as "Blue Zones," have been identified as the areas with the highest percentage of centenarians (**Figure 1**) (1). High longevity rates of Ikaria residents stimulated the conduction of a thorough epidemiological study (the IKARIA study) aiming to examine population's individual characteristics and habits that could be related to exceptional longevity. In the context of the IKARIA study, pathophysiological mechanisms of cardiovascular aging and longevity, their interaction, and their translation into lifestyle behaviors are discussed in the present review.

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## PATHOPHYSIOLOGICAL LINKS BETWEEN CARDIOVASCULAR AGING AND LONGEVITY

The most important known pathophysiological links between cardiovascular aging and longevity are presented in **Table 1**.

**OXIDATIVE STRESS.** Increased oxidative stress, expressed as alterations in the balance between reactive oxygen species (ROS) production and antioxidant defenses, is considered an important mechanism involved in the aging process and has been linked to the pathogenesis of many age-related diseases, including cardiovascular disease (CVD). According to the "free radical theory of aging," aging is the result of accumulative oxidative damage of cellular constituents (2). Increased oxidative stress can cause mitochondrial DNA mutations and damage

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 29, 2020; revised manuscript received November 12, 2020, accepted November 13, 2020.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.11.023

**ABBREVIATIONS AND ACRONYMS**

**AMPK** = adenosine monophosphate-activated protein kinase

**APOE** = apolipoprotein E

**BP** = blood pressure

**CHIP** = clonal hematopoiesis of indeterminate potential

**CR** = calorie restriction

**CRP** = C-reactive protein

**CVD** = cardiovascular disease

**FMD** = flow-mediated dilation

**FOXO** = forkhead box protein O

**HMG-CoAR** = 3-hydroxy-3-methylglutaryl-coenzyme A reductase

**IGF** = insulin-like growth factor

**LDL-C** = low-density lipoprotein cholesterol

**mTOR** = mammalian target of rapamycin

**NF-κB** = nuclear factor-kB

**PWV** = pulse wave velocity

**ROS** = reactive oxygen species

in other mitochondrial constituents, resulting in impairment of electron transport chain function, increase in mitochondrial permeability, and therefore mitochondrial and overall cellular dysfunction (3,4). Efficacy of antioxidant mechanisms and resistance to oxidative stress are believed to decline with increasing age (4). All these can lead to cellular senescence or apoptosis as means of protection from the harmful impact of persistent oxidative stress or cellular necrosis due to extensive oxidative damage, thus, promoting the aging process (3–5).

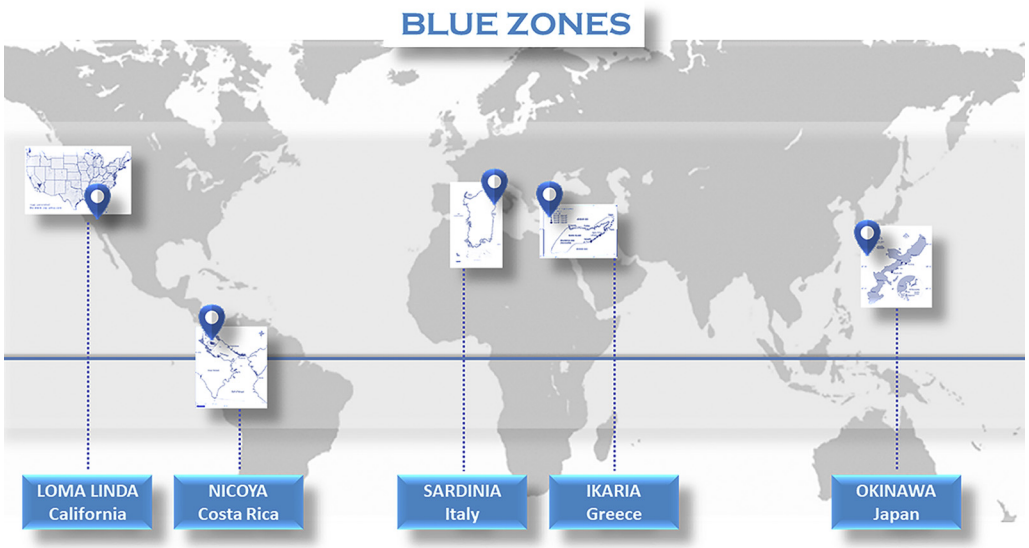
The important role of oxidative stress in aging and determination of life span duration is supported by a considerable body of evidence. Increased activity of the antioxidants superoxide dismutase and catalase and increased resistance to oxidative stress were associated with prolonged life span in *Caenorhabditis elegans*, *Drosophila*, and mice (6,7). Moreover, experimental studies focusing on the effects of oxidative stress on the cardiac tissue have shown that inhibition of type 5 isoform of adenyl-cyclase (AC-5), which plays a key role in sympathetic transmission and beta-adrenergic receptor signaling in the heart, increases resistance to oxidative stress in mice through upregulation of superoxide dismutase, resulting in protection from cardiomyopathy induced by various stressors and in extension of life span by 30% (8).

In humans, several studies have reported reduced levels of markers of oxidative stress and/or increased

**HIGHLIGHTS**

- Cardiovascular aging and longevity share common pathophysiological mechanisms.
- Delaying cardiovascular aging increases the likelihood of longevity.
- Mediterranean diet, low-calorie intake, physical activity, smoking cessation, and a favorable genetic and environmental background are features of long-living populations.
- The areas of the world with high longevity records may serve as a model for investigations of genetic and pathophysiological mechanisms and for the evolution of the field of rejuvenation medicine.

**FIGURE 1** The Blue Zones




Five places on earth have been identified as places with the highest longevity rates; they are so-called "Blue Zones." Epidemiological findings from these areas, especially from the Greek eastern Aegean island of Ikaria, highlight the relationship between cardiovascular aging and longevity.

**TABLE 1 Potential Pathophysiological Links Between CV Aging and Longevity**

| |
|---|
| Oxidative stress |
| Inflammatory activation |
| Metabolic disorders |
| Hyperglycemia |
| Hyperinsulinemia |
| Insulin resistance |
| Dyslipidemia |
| Vascular disorders |
| Endothelial dysfunction |
| Arterial hypertension |
| Arterial stiffness |
| Genetic-epigenetic mechanisms |
| Telomere length |
| DNA methylation |
| Clonal hematopoiesis of intermediate potential (CHIP) |

CV = cardiovascular.

levels of antioxidant molecules in long-lived individuals compared with elderly of younger age (9,10). Investigators found higher levels of antioxidant vitamins C and E and lower levels of reaction products of malondialdehyde with thiobarbituric acid and lipid hydroperoxides in healthy centenarians compared with elderly participants of younger age (9); a similar pattern was evident in other studies with Italian centenarians (10). Okinawan centenarians also presented lower levels of lipid peroxidation compared with younger individuals of various age groups (11). Others demonstrated a generally maintained antioxidative status in healthy nonagenarians compared with young controls (12), whereas Spanish researchers showed that levels of oxidative stress were lower in elderly individuals >97 years old than in controls age 70 to 80 years (13). Genetic analysis in a large sample of nonagenarians in Denmark demonstrated a significant association of antioxidant-related genetic polymorphisms with increased survival beyond 90 years (14). These findings were partially replicated in an Italian elderly cohort (15).

However, in a number of experimental studies, oxidative stress was not inversely related with duration of life span, and genetic and pharmaceutic interventions in animals aiming to prolong life span through attenuation of oxidative stress did not produce the expected results (16). Moreover, there is strong evidence of the existence of the "mitohormesis" phenomenon; the promotion of stress resistance and longevity after exposure to non-lethal ROS concentrations (17). Recently, investigators demonstrated that a transient increase in ROS, which occurs naturally in the early development of *C. elegans,* increases stress resistance, improves redox homeostasis, and prolongs life span, an effect that is linked with the ROS-mediated decrease in developmental histone H3K4me 3 levels (18).

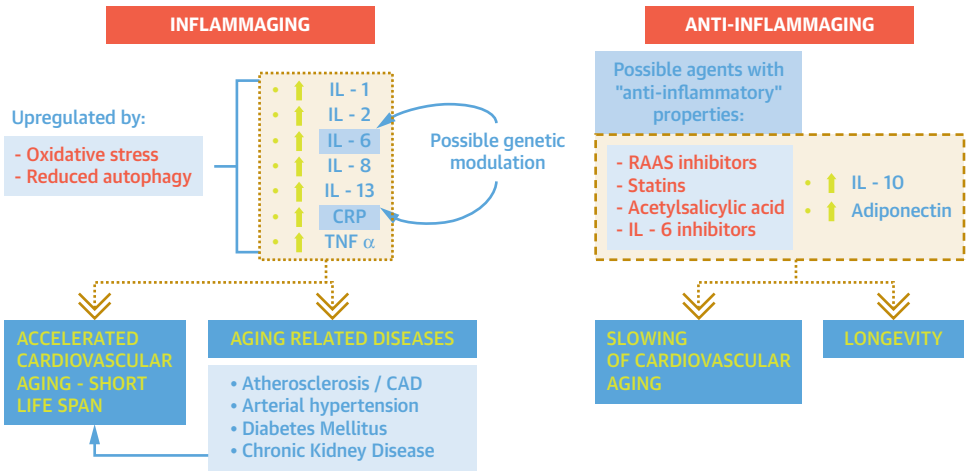
Thus, future research should target pinpointing the subtle in vivo balance between preoxidant and antioxidant processes, either naturally or pharmaceutically, which might be the key for an optimal oxidative status that will both delay cardiovascular aging and promote longevity.

**INFLAMMATORY ACTIVATION.** The role of low-grade inflammation as a pathophysiological mechanism and risk factor for many aging-related diseases, including CVD, has been highlighted by several studies (19). Importantly, the term "inflammaging" has been introduced in the published data as a distinct pathophysiological entity aiming to describe the chronic progressively increasing proinflammatory status that characterizes the aging process (20) (**Figure 2**). Moreover, it has been proposed that a successful response to low-grade inflammation ("anti-inflammaging") could underlay longevity (**Figure 2**). Similar to oxidative stress, maintaining a proper equilibrium between pre-inflammatory and anti-inflammatory agents, thus providing adequate protection from infections and concurrently avoiding high levels of chronic inflammation, may be of great importance.

Proinflammatory molecules that have mostly been identified to participate in the inflammatory state are interleukins (ILs) such as IL-1, IL-6, IL-8, IL-13, IL-18, C-reactive protein (CRP), and tumor necrosis factor-α and its receptors (19) (**Figure 2**). Numerous studies have reported associations between these cytokines and several age-related diseases. Accordingly, associations with related genes, mainly modulating CRP and IL-6 expression, also have been observed (21). Importantly, higher levels of inflammatory markers have been negatively related with longevity in elderly populations (22). Conversely, anti-inflammatory molecules may be protective; for example, a genetic variant promoting synthesis of the anti-inflammatory IL-10 has been associated with longevity in Italian centenarians (23), whereas Van Den Biggelaar et al. (24) have shown that lower IL-10 levels and a polymorphism related with lower IL-10 production were predictive of higher CV mortality.

Among other molecular mechanisms that are implicated in inflammaging is the activation of the nuclear factor NF-κB. Activation of the NF-κB results in upregulation of proinflammatory genes and increased expression of several cytokines (25). Interestingly, in a study that used motif mapping of genes,

**FIGURE 2 Inflammation, CV Aging, and Longevity**




The term "inflammaging" refers to the inflammatory activation that occurs with aging and is associated with aging-related diseases, including atherosclerotic cardiovascular disease, and short life span. On the contrary, "anti-inflammaging" is a state induced by "anti-inflammatory" cytokines, such as interleukin-10. Agents with anti-inflammatory properties may be proposed as inducers of "anti-inflammaging." "Anti-inflammaging" contributes to better cardiovascular health and longevity. CAD = coronary artery disease; CRP = C-reactive protein; CV = cardiovascular; IL = interleukin; RAAS = renin angiotensin aldosterone system; TNF = tumor necrosis factor.

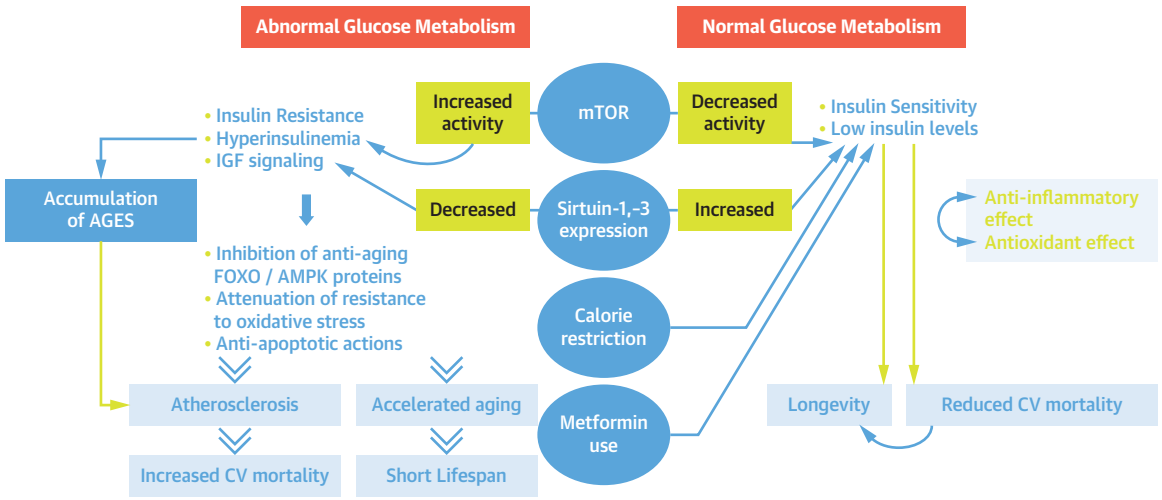
the NF-κB motif was most strongly related to aging (26), whereas NF-κB inhibition was found to prolong survival in experimental studies (27). With aging, an increasing number of human cells undergo senescence, a condition mainly referring to loss of proliferative capacity. Cell senescence is mostly a defense mechanism against oncogenesis and cell injury, which is more likely to occur with advancing age (28). Senescent cells present a senescence-associated secretory phenotype, which causes activation of NF-κB and secretion of proinflammatory cytokines and matrix metalloproteinases (MMPs) that can either exert paracrine inflammatory actions or escape in the circulation and maintain low-grade inflammation (28).

An important source of inflammation in aged subjects is fat, especially visceral fat. An increasing total lipid amount and a fat redistribution, from the subcutaneous to the visceral fat, are observed with aging. Visceral fat is infiltrated by inflammatory cells and secretes cytokines and proinflammatory hormones, such as leptin. Gut microbiota has emerged as another possible contributor to inflammaging. Presence of "normal" gut microbiota is considered a protective mechanism that prevents expansion of potentially harmful microorganisms (19); however, with increasing age, alterations in the composition of gut microbiota have been demonstrated along with increased intestinal mucosal permeability, which could allow entrance of bacteria and/or cytokines in the circulation (19).

Specifically for CVD, inflammation is now recognized as a pivotal feature that promotes atherosclerosis. Pharmaceutical treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, and acetylsalicylic acid decreases cardiovascular mortality, an effect that may be, partly, mediated by the anti-inflammatory properties of these agents. Interestingly, RAAS inhibitors and statins have shown to increase life span in animal models, thus exerting antiaging effects (29,30). Recently, canakinumab, a monoclonal antibody targeting IL-1b, therefore indirectly inhibiting the IL-6 pathway, reduced major CV events (albeit at the cost of an increase in fatal infections), providing robust evidence that targeted inflammatory therapy can be beneficial in CVD (31). Future studies need to establish the role of agents with anti-inflammatory effects in the delay of aging and promotion of longevity.

**METABOLIC DISORDERS. Hyperglycemia and insulin disturbances.** Hyperglycemia promotes aging through many biochemical pathways. In invertebrates, high glucose conditions accelerate aging via downregulation of proteins known to promote longevity, such as the adenosine monophosphate-activated protein kinase (AMPK) and the forkhead

**FIGURE 3** Glucose Metabolism and Longevity




Abnormal glucose metabolism, defined as hyperglycemia, hyperinsulinemia, and insulin resistance, contributes to accelerated cardiovascular aging but also to short life span through several pathophysiological mechanisms, such as inhibition of antiaging proteins. Moreover, disrupted regulation of molecules related to longevity (such as mammalian target of rapamycin and sirtuins) have been related to abnormal glucose metabolism, thus demonstrating a bidirectional relationship between longevity and abnormal glucose metabolism. On the contrary, normal glucose metabolism with insulin sensitivity and low insulin levels is associated with decelerated cardiovascular aging and longevity. AMPK = adenosine monophosphate-activated protein kinase; CV = cardiovascular; FOXO = forkhead box protein O; IGF = insulin-like growth factor; mTOR = mammalian target of rapamycin

box protein O (FOXO) transcription factor DAF-16 (28). Increased activity of AMPK has been found to extend life span in *C. elegans*, through favorable modulation of mitochondrial function and lipid metabolism (32). The FOXO DAF-1 belongs to the family of FOXO transcription factors, which control several cellular important functions, including metabolism, oxidative stress resistance, and apoptosis, and are believed to be implicated in aging and longevity (33). Activity of FOXO DAF-16 is inhibited by the insulin/insulin-like growth factor 1 (IGF-1) pathway, which is upregulated after exposure to high glucose (28).

As for mammals, many studies have shown that exposure to hyperglycemia induces senescence of several types of cells, such as endothelial progenitor cells, vascular smooth muscle cells, and renal tubular cells (34). Augmented oxidative stress and increased production and accumulation of advanced glycosylation end products are considered primary mechanisms linking hyperglycemia with aging and age-related diseases, such as atherosclerotic CVD (32). Indeed, Chen et al. (35) showed that glycated collagen accelerated senescence in cultured human endothelial cells, whereas others reported that advanced glycosylation end products induced calcification in vascular smooth muscle cells (36) and exerted pro-aging effect on renal cells (37).

Reduced activity of sirtuins could also play a crucial role in hyperglycemia-induced aging. Sirtuins (sirtuin-1 to sirtuin-7) are NAD-dependent enzymes that control important cellular functions in several sites inside the cell, enhancing the metabolic homeostasis preservation and cellular damage repair. Indeed, data have shown that polymorphisms in sirtuin-3 and siruin-1 genes are associated with human longevity (38,39) (**Figure 3**). Cultures of human endothelial cells exposed to high glucose concentrations presented signs of early senescence along with significant reduction in the expression of sirtuins (40). Increased glucose availability (e.g., due to high intake) can result in enhanced glycolytic activity, during which NAD is consumed for the production of NADH. Because sirtuins are NAD-dependent enzymes, diminished NAD levels eventually result in reduced activity of sirtuins, thus exerting a pro-aging effect (41).

Insulin, insulin resistance, and the insulin/IGF-1 pathway are also important factors in the aging process. Indeed, both animal and human studies indicate that normal glucose metabolism, lower insulin levels, and higher insulin sensitivity could constitute a

marker of healthy aging and longevity (42) (**Figure 3**). Adiponectin, a protein secreted by the adipose tissue that enhances insulin sensitivity and exerts anti-inflammatory properties, has also been found upregulated in individuals >95 years old (43). Conversely, increased insulin/IGF-1 signaling has been associated with aging, through inhibition of antiaging FOXO proteins, attenuation of resistance to oxidative stress, and exertion of possible antiapoptotic actions that may be related to development of cancer (44). Importantly, insulin and IGF-1 stimulate activation of the mammalian target of rapamycin (mTOR), a protein kinase that is a member of the kinase family PI3KK (phosphatidylinositol 3 kinase-related kinase), and is found in almost every eukaryotic organism (45). Furthermore, mTOR regulates numerous cellular functions, including apoptosis, oxidative stress response, and senescence, and is considered a major contributor to aging, whereas reduced mTOR activity has been linked to life span extension (45) (**Figure 3**). However, it should be noted that mTOR has 2 distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) with different functions and sensitivity to rapamycin. Indeed, although the inhibition of mTORC1 may promote longevity, the inhibition of mTORC2 may have negative results, partly through increasing insulin resistance (46). An mTOR inhibitor that induces an incomplete inhibition of mTORC1 but spares mTORC2, has been proposed as the most appealing candidate for mTOR inhibition and, thus, life span extension (47).

Interestingly, in the era of modern antidiabetic therapies, an old but effective choice, metformin, which acts as an insulin-sensitizing agent that activates AMPK and also has anti-inflammatory and antioxidant properties, has been proposed by researchers as a drug with potential antiaging properties (48) (**Figure 3**).

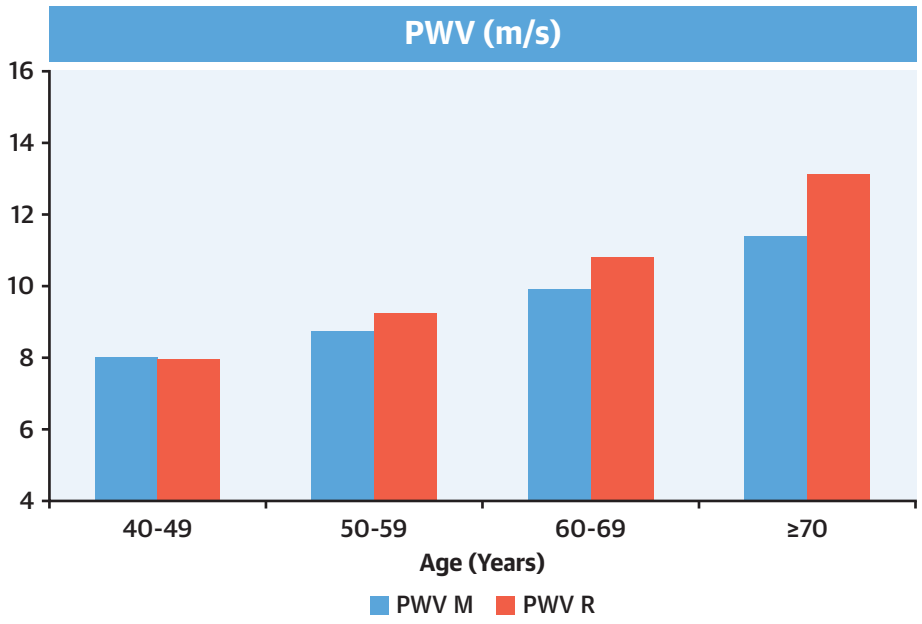
**Dyslipidemia.** Several age-related mechanisms are believed to mediate alterations in lipoprotein synthesis and activity resulting in dyslipidemia. Adipose tissue is a dynamic endocrine gland with important functions, such as energy deposit, temperature regulation, nutritional handling, secretion of vasoactive substances, immune system modulation, and tissue remodeling (49). With increasing age, total amounts of body fat and especially visceral fat, increase, therefore predisposing to reduced insulin sensitivity, low-grade inflammation, and production of atherogenic lipoproteins (50). Interestingly, in experimental studies, increased expression of the potentially antiaging enzyme sirtuin-1 was associated with lower low-density lipoprotein cholesterol (LDL-C) and insulin levels and reduced obesity-induced insulin resistance (51). Another animal study reported that a pharmacological activator of sirtuin-1 reduced LDL-C and total cholesterol levels and ameliorated atherosclerosis in mice fed a high-cholesterol diet; these findings were attributed to reduced expression of proprotein convertase subtilisin/kexin type (9PCSK9), which is known to promote degradation of LDL-receptor and, thus, inhibit LDL-C uptake (52).

The aging-observed hypercholesterolemia also may be partially attributed to reduced degradation and increased activation of the enzyme that is pivotal for cholesterol biosynthesis, the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoAR); reduced insulin sensitivity also may be involved in this biochemical pathway (53). Notably, in aged rats, the process of reduced degradation of HMG-CoAR was regressed after calorie restriction (54).

Finally, the genetic modulation of lipoproteins is implicated in the inverse relationship between atherosclerosis and longevity. Polymorphisms of the gene encoding apolipoprotein E (APOE), a major regulator of lipid metabolism, have been related to longevity. APOE has several isoforms, among which APOE4 and APOE3 are the most common, although ApoE2 and even rarer ones also exist. The difference in the interaction of their amino acids affect the structures and their impact on disease. Indeed, the APOE4 isoform is linked to increased LDL-C levels (55) and the corresponding allele is related to reduced odds of achieving longevity and increased odds of developing CVD and Alzheimer disease compared with the allele promoting synthesis of APOE3 (56). Other studies reported that genetic predisposition to high LDL-C values is associated with higher mortality risk, even in ages >90 years, whereas a favorable LDL-C genetic profile is related to familial longevity (57). Finally, a genetic study in long-lived Ashkenazi Jewish individuals (mean age 98 years) provided evidence that size of lipoprotein particles could play a role in the longevity observed in this population. Elderly participants and their offspring had significantly larger LDL-C and high-density lipoprotein cholesterol particle sizes compared with the general population, whereas the increased particle size was associated with reduced prevalence of arterial hypertension, metabolic syndrome, and CVD (58).

**ARTERIAL HYPERTENSION-ARTERIAL STIFFNESS.** The main primary vascular disorders considered to be implicated in the aging process are hypertension and arterial stiffness, which are linked through a cause-and-effect relationship. Arterial hypertension

**FIGURE 4** **Aortic Stiffness and Longevity**




Difference in pulse wave velocity (PWV) between Ikaria inhabitants (PWV M) and the reference population (PWV R). After the age of 50 years, PWV was constantly and significantly lower in Ikaria inhabitants compared with the general population, implying a possible deceleration of vascular aging. From Pietri P, Vlachopoulos C, Chrysohoou C, et al. Deceleration of age-related aortic stiffening in a population with high longevity rates: the IKARIA study. J Am Coll Cardiol 2015;66:1842–3.

promotes arterial stiffness and vice versa. Arterial hypertension is an established risk factor for CVD and clearly an aging-related disease (59), whereas increasing evidence suggests that it is associated with subclinical inflammation (60), thus reinforcing the notion of "inflammaging."

Notably, genetic polymorphisms related to low blood pressure (BP) values, have been linked to longevity. A meta-analysis of genetic studies in 7,729 elderly subjects (≥85 years) and 16,121 individuals of younger age (<65 years), demonstrated an important association between a novel locus (rs2149954 in the 5q33.3 chromosome) and survival beyond 90 years (61). Interestingly, carriers of the minor allele of rs2149954 (T) on chromosome 5q33.3 had lower cardiovascular mortality risk, driven mainly by the protection from stroke (61). Moreover, this allele had been previously linked with low BP in middle age (61). Other researchers showed that the presence of rs198389, a functional variant in the promoter region of the B-type natriuretic peptide (BNP) gene (*NPPB*) was related to high levels of N-terminal pro-BNP (NT-proBNP) during adulthood, decreased arterial BP, reduced CV mortality, and life extension (62).

Arterial hypertension contributes to arterial aging. Arterial stiffness is the core of early vascular aging syndrome, a novel concept that aims to elucidate mechanisms of early and/or accelerated vascular aging and identify individuals with the respective phenotype (63). Measurement of pulse wave velocity (PWV), especially carotid-to-femoral pulse wave velocity (cf-PWV), is the gold-standard surrogate marker of arterial stiffness. Moreover, low-grade inflammation is implicated into the pathophysiology of aortic stiffness (64,65), thereby further fueling the "inflammaging" concept, whereas oxidative stress may also contribute to loss of arterial elasticity through tissue injury and NO depletion. Noteworthy, arterial stiffness is an independent predictor of CV events and CV and all-cause mortality (66). The genetic predisposition to elastic arteries and longevity cannot be excluded given that parental longevity has been associated with lower PWV values in adult offspring compared with those whose father did not live longer than 80 years (67). Interestingly, in the IKARIA study, PWV was significantly lower in inhabitants aged >50 years as compared with individuals of the same age groups in the general population (68) (**Figure 4**), a finding that implies a

deceleration in vascular aging, which may have important clinical implications for CV health and longevity. A positive effect of genetic, environmental and lifestyle factors on the favorable vascular function of this population is possible, but warrants further investigation.

## GENETIC-EPIGENETIC MECHANISMS

**TELOMERE LENGTH.** Telomeres are DNA-protein complexes that cap both ends of each chromosome and play a pivotal role in maintaining chromosomal stability and integrity. During life, most cells are subject to several divisions, and DNA replication is an essential step in each division. DNA polymerases, a family of enzymes responsible for DNA replication, are unable to induce replication of the whole chromosome (i.e., replication until chromosome ends), a condition known as the "end replication problem" (69). Telomeres protect chromosome ends from degradation during replication. However, length of telomeres is reduced after each cell division as a consequence of the end replication problem; moreover, telomere shortening is believed to be accelerated by conditions like increased oxidative stress and inflammation (3) (**Figure 5**). Telomere shortening is partially counterbalanced by telomerase, a ribonucleoprotein complex that binds to the telomere and promotes synthesis of telomeric sequences. After a certain number of cell divisions, telomeres may have been shortened to a critical extent and have lost their protective properties and these may induce cell senescence, loss of ability to proliferate, and/or apoptosis, thus, constituting a major mechanism involved in the aging process (69). Under this prism, telomeres have been characterized as "biological clock," a term that emphasizes their important role in modulation of cell life span. The anti-oncogenic p53 pathway is largely involved in termination of division and in apoptosis of cells with critically short telomeres. In case of p53 mutation or loss of function, these cells may escape arrest of division and continue to divide until reaching the stage of crisis, that is, extensive fusion of chromosome ends and genome instability and subsequent massive cellular death (70) (**Figure 5**).

Short telomere length has been related to several CV risk factors and age-related diseases (**Figure 5**). In the MacArthur Health Aging Study, absolute baseline telomere length was inversely associated with CV mortality in elderly women, whereas telomere shortening during follow-up was related to increased CV mortality in elderly men (71). Moreover, telomere-related polymorphisms were linked with CV mortality in women in the Cardiovascular Health Study (72). Importantly, a recent meta-analysis conducted in the general population demonstrated significant associations between short telomere length and all-cause mortality (73).

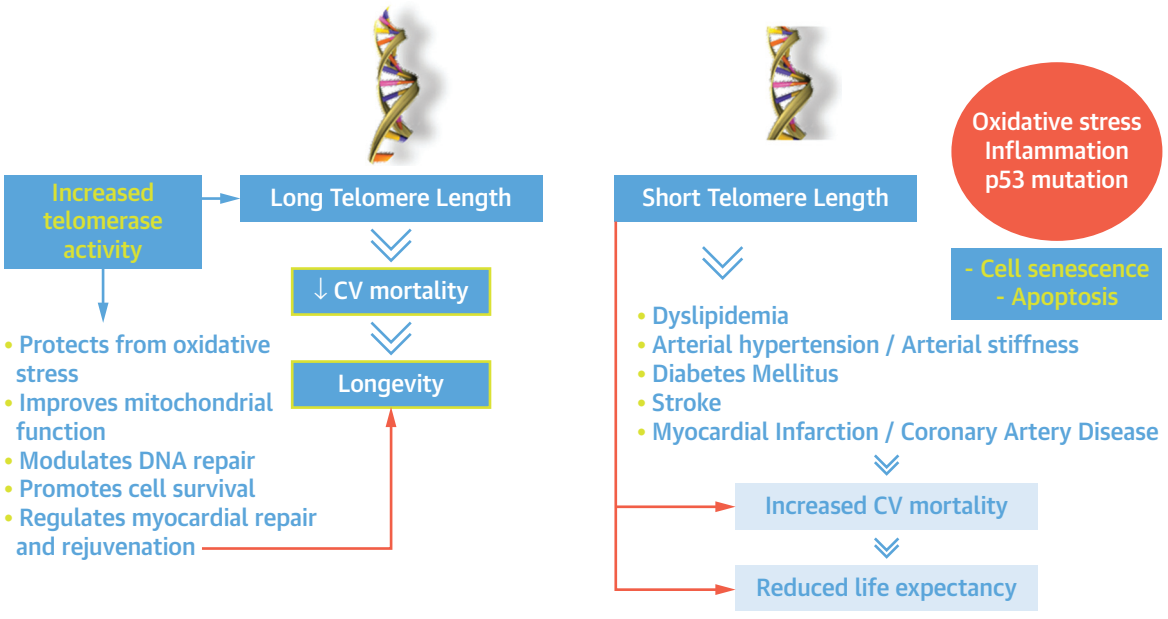
Increased telomerase activity is probably an important factor contributing to higher length of telomeres and achievement of longevity (**Figure 5**). Telomerase has 2 essential components, the reverse transcriptase component (hTERT) and the RNA component (hTERC). Data from an elderly Swedish cohort suggest that a genetic polymorphism implicated in the synthesis of hTERT, the catalytic subunit of telomerase associated with increased telomerase activity, was related to older age at death in women (74). In the mammalian heart, the expression of telomerase is small, but functionally significant. In mice, a population of cells with features of cardiomyocytic, endothelial, and mesenchymal phenotype was identified as responsible for telomerase activity. This cell population with telomerase activity presented a 6.45-fold increase, compared with control adult hearts, after myocardial cryoinjury, suggesting that telomerase may play a regulatory role on the myocardial repair and rejuvenation (75). In other experimental studies, activation of telomerase after myocardial infarction reduced the risk of heart failure and increased survival, whereas loss of telomerase resulted in occurrence of features observed in heart failure, that is, ventricular dilatation, wall thinness, and increased apoptosis (76).

In addition, accumulating evidence suggests that telomerase might exert an antiaging effect through nontelomeric activities. Therefore, telomerase has been found to confer protection from oxidative stress, improve mitochondrial function, modulate DNA repair, inhibit apoptotic process, and promote cell survival independent of telomere elongation (77) (**Figure 5**). The nontelomeric effects of telomerase, attributed to hTERT expression, remain, however, disputed (78). Therefore, the exact role of telomerase on cardiovascular aging and longevity needs further investigation.

To conclude, telomere length is important for both cardiovascular aging and longevity, whereas the predominant effect on cardiovascular aging is attributed to the modulation of atherosclerotic CV disease (79).

**DNA METHYLATION CLOCKS AND CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL.** In an effort to discover more about the epigenetic substrate of aging and longevity and to better define biological age, the term of "epigenetic" or "DNA

**FIGURE 5** **Telomeres, CV Aging, and Longevity**

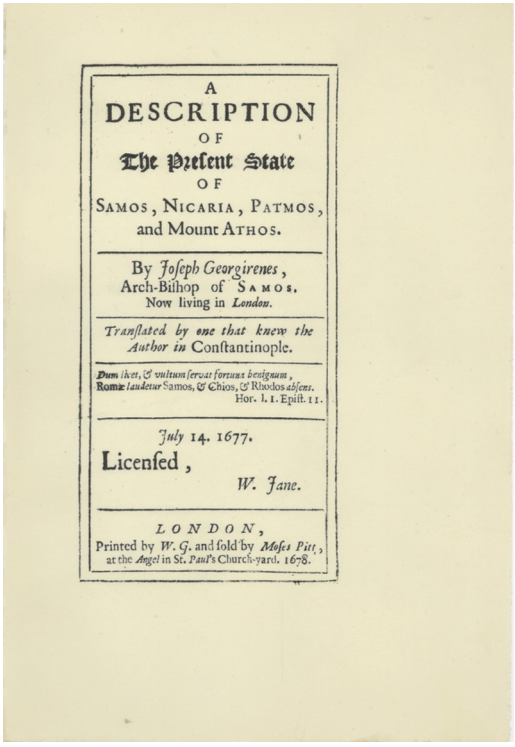



Short telomere length is associated with many aging-related diseases that promote cardiovascular aging and increased cardiovascular mortality. Short telomere length is also associated with short life span. Oxidative stress and low-grade inflammation, the 2 most recognizable underlying pathophysiological mechanisms of atherosclerotic CV disease, seem to accelerate shortening of telomere length. On the contrary, long telomere length has been associated with both decreased CV mortality and longevity. Increased telomerase activity, through increase in the length of telomeres but also through telomere-independent mechanisms, contributes to longevity. CV = cardiovascular.

methylation clocks" has been recently introduced. DNA methylation is a common phenomenon in organisms, and describes the methylation of DNA's bases, predominantly at the site of cytosine (5-methylcystosine, 5mC). In mammalian cells, DNA methylation is found almost exclusively in the CpG dinucleotide sequence context and plays an important role in gene expression regulation, development, and disease, whereas age-related changes in DNA methylation are implicated in healthy aging and longevity (80). Loss of DNA methylation at certain loci has led to epigenetic clocks of aging. Among research groups on "epigenetic clocks," Hannum et al. (81) constructed a predictive model of aging rate using measurements at more than 450,000 CpG markers from the whole blood of humans, whereas Horvath (82) developed a multitissue predictor of age that allows the estimation of DNA methylation age of most tissues and cell types. Investigators showed that the difference between Horvath's estimated biological age and chronological age was associated with incident CVD in 832 older individuals after 10 years of follow-up (83). Whether these "epigenetic clocks" may accurately estimate vascular age and, thus, serve as a biomarker of CVD is a challenge that remains to be addressed (84).

Novel research on the genetic modulation of aging has focused on the role of clonal hematopoiesis of indeterminate potential (CHIP). The CHIP phenomenon refers to a mutation process of hematopoietic stem cells. Hematopoietic stem cells divide continuously during our lifetime and as a consequence of this mitotic activity, mutations can occur. Most of these mutations lead to cell death, but occasionally a mutation promotes cell survival and, thus, a clonal expansion of the mutated cells is created. The "immortalized" clone of these blood cells represents the phenomenon of CHIP. The most common mutations related to CHIP are in 4 genes: DNMT3A, TET2, ASXL1, and JAK2, all of which are associated with CVD (85). Moreover, these genes are implicated in the control of inflammation through regulation of proteins of the innate immune system responsible for inflammatory stimulation, known as *inflammasome*. Study in mice showed that these inflammasome genes may accelerate atherosclerosis through inflammatory activation (86). Interestingly, IL-1β (the monoclonal antibody against IL-1β was used in the

**FIGURE 6 The Book of Longevity**


A
DESCRIPTION
OF
The Present State
OF
SAMOS, NICARIA, PATMOS,
and Mount ATHOS.

By *Joseph Georgirenes*,
Arch-Bishop of SAMOS,
Now living in *London*.

*Translated by one that knew the Author in* Constantinople.

*Dum iket, & vultum servat fortuna benignum,*
*Roma laudetur* Samos, & Chios, & Rhodos *absens.*
Hor. l. 1. Epist. 11.

*July* 14. 1677.
Licensed,
*W. Jane.*

*LONDON*,
Printed by *W. G.* and sold by *Moses Pitt*,
at the *Angel* in St. *Paul's* Church-yard. 1678.

The cover of the book written by Archbishop Joseph Georgirenes and published in London, in the 17th century. He describes, for the first time, the unique phenomenon of longevity on Ikaria island.

CANTOS Study [Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events)]), is associated with CHIP, whereas the expression of the mutated inflammasome genes related to IL-1β production has been associated with increased oxidative stress, arterial hypertension, arterial stiffness, and all-cause mortality in older individuals (87). Research on the challenging role of CHIP on age-related diseases is only recently developed and future studies need to establish the etiological relationship, if any, between CHIP and longevity and thus, to move one step forward into personalized medicine.

## LIFESTYLE BEHAVIORS THAT MAY PROMOTE LONGEVITY

**HEALTHY DIET.** A huge amount of scientific research has dealt with the impact of nutrition on longevity. The so-called Mediterranean diet is probably the most studied dietary pattern, and several studies have highlighted its beneficial effect on CV and holistic health. The epidemiological study that established for the first time an inverse relationship between Mediterranean diet and CV mortality was the Seven Countries Study in the late 1950s-early 1960s (88,89). A subsequent study in a large sample of the Greek population demonstrated after 44 months of follow-up a significant inverse relationship between Mediterranean diet and mortality (90).

In the IKARIA study, in a sample of elderly subjects aged older than 80 years, a significant adaptation to the Mediterranean diet was observed (91). The CV protection conferred by the Mediterranean diet is attributed to favorable modulation of classic CV risk factors but also to amelioration of other factors related with CVD and aging, such as inflammation, oxidative stress, and endothelial dysfunction (92). These actions are exerted either as a whole, implying a beneficial food synergy (e.g., in the IKARIA study level of adherence to the Mediterranean diet was inversely related to uric acid levels, which might serve as marker of oxidative stress [93]) or due to specific properties of separate components.

There is evidence that coffee intake could be another dietary factor contributing to longevity. Elderly participants of the IKARIA study were, at the largest proportion, moderate coffee consumers (200 to 450 ml/day) (91). Assessment of endothelial function with flow-mediated dilation (FMD) in inhabitants aged >65 years demonstrated a linear relationship between increasing coffee consumption and higher FMD values (94). Coffee contains polyphenols and micronutrients (e.g., vitamins), which act as antioxidants and it also has anti-inflammatory properties. Moreover, caffeine, the polyphenol chlorogenic acid contained in coffee, and its metabolites caffeic and ferulic acid have been shown to improve NO metabolism and vascular function, whereas another study has reported that coffee can inhibit platelet aggregation (95). Most importantly, coffee consumption has been related to improved clinical outcomes. In the EPIC (European Prospective Investigation into Cancer and Nutrition) study, increased coffee consumption was associated with lower total mortality in both genders and lower CV and stroke-related mortality in women after a 16-year follow-up (96). Moreover, a recent large meta-analysis concluded that moderate coffee intake (2 to 4 cups per day) was associated with significantly reduced all-cause mortality (by 15%), CV mortality (by 17%), and cancer mortality (by 4%) (97). In the IKARIA study, coffee drinking, along with fruit intake and olive oil consumption, was associated with decreased incidence of CVD (98).

Another dietary approach extensively studied and potentially linked with longevity is calorie restriction (CR). A large amount of evidence in nonhuman studies indicates that reduction in energy intake by 20% to 40% promotes life span extension (99). Moreover, the longevity of Okinawans in Japan has been largely attributed to CR; 4 decades ago, it had been estimated that Okinawans had 17% lower calorie intake compared with the average intake in Japan and presented remarkably lower mortality from age-related diseases and higher life span duration (100). Elderly inhabitants of Ikaria also reported a relatively low daily energy intake (91). In several studies, from yeasts to mammals, CR has been linked with increased activity of AMPK and sirtuins, inhibition of mTOR, activation of FOXO proteins, reduced oxidative stress and inflammation, and improved insulin sensitivity, all of which potentially promote longevity (101). However, the effects of CR on human longevity remain obscure. Recently, the low-protein, low-calorie fasting-mimicking diets gain attention due to their antiaging properties, safety, and feasibility, although clinical studies are limited (102).

It is of note that aspirin, a cardiovascular drug with anti-inflammatory and antithrombotic properties has been recognized as a calorie-restriction mimetic, mainly by inducing autophagy (103).

In conclusion, the Mediterranean diet, possibly accompanied by coffee intake, seems the most appropriate dietary choice for CV and holistic health. Low-calorie intake is also a promising dietary path to longevity.

**PHYSICAL ACTIVITY.** Physical activity and exercise are considered essential factors contributing to healthy aging and prolonged life span. Approximately 90% of men and 70% of women aged >80 years in the IKARIA study reported moderate or high daily physical activity (91), a feature that was common among inhabitants from the blue zone of Sardinia (104). Moreover, in the IKARIA study, endothelial function assessed by FMD was significantly improved in middle-aged subjects who reported regular exercise compared with those who did not exercise (105). In the Physicians' Health Study, regular exercise was related to higher probability of reaching the age of 90 along with better functional status at late life (106).

Several aging-related mechanisms mediate the benefits associated with physical activity and exercise. Physical activity promotes CV health through reduction of the burden of established CV risk factors (i.e., hypertension, hyperglycemia, dyslipidemia). These factors probably do not fully account for the protection conferred by physical activity. Exercise influences coagulation mechanisms and shifts the balance toward a less thrombogenic status (107). Moreover, physical activity attenuates inflammation and oxidative stress and improves endothelial function (108,109).

Furthermore, there is evidence that exercise could exert antiaging properties through an effect on telomere length. A positive relationship between level of physical activity and telomere length in a study with 2401 twin volunteers was demonstrated (110), whereas others reported increased presence of longer telomeres in athletes compared with controls (111), along with upregulated telomerase activity in one of them. Notably, increased telomerase activity observed in mice after short-term exercise was accompanied with reduced expression of the apoptotic proteins p16 and p53 (112).

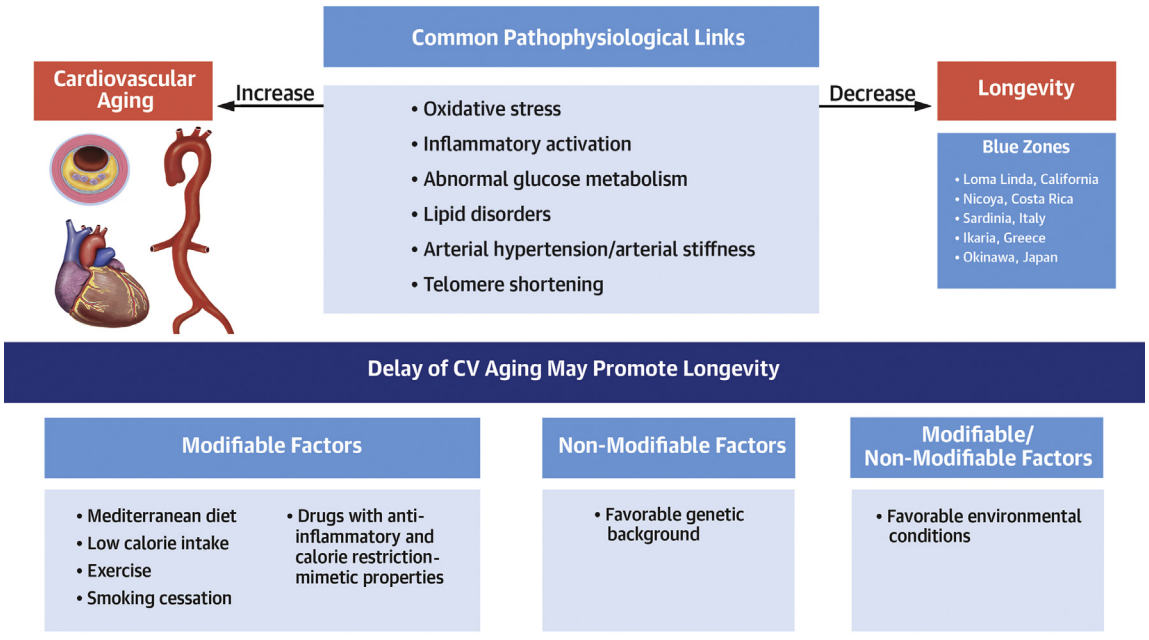
**SMOKING CESSATION.** Apart from the beneficial effects of exercise on CV and holistic health, abstaining from smoking is fundamental for healthy aging and longevity. Smoking is a strong, modifiable CV risk factor, even among older adults (113). In the elderly Ikaria inhabitants, the percentage of active smokers was low (17% in men, 7% in women), although 82% of men were former smokers (91). Smoking cessation reduces CV risk (113), although there is uncertainty about the time course of CV risk reduction following smoking cessation. Recently, in a prospective analysis from the Framingham Heart Study, smoking cessation, among heavy smokers, was associated with a significantly lower risk of CV events within 5 years, relative to current smokers (114). However, ex-smokers had significantly increased cardiovascular risk, beyond 5 years after smoking cessation, compared with never smokers (114). In another study, smoking cessation after a first CV event was associated with lower risk of recurrent CV events and all-cause mortality (115). Among other mechanisms, beneficial alterations in endothelial function may partially explain the decreased CV risk associated with smoking cessation (116).

Therefore, physical activity and smoking cessation reduce CV risk and may favorably modulate duration of life span.

## ENVIRONMENT, CARDIOVASCULAR AGING, AND LONGEVITY

Environmental conditions constitute another factor potentially influencing CV risk and overall life expectancy.

**CENTRAL ILLUSTRATION** Cardiovascular Aging and Longevity




**Pietri, P. et al. J Am Coll Cardiol. 2021;77(2):189–204.**

Cardiovascular aging and longevity are interrelated through common pathophysiological links, such as oxidative stress, low-grade inflammation, and insulin resistance. Moreover, lipid disorders, arterial hypertension, and arterial stiffness accelerate cardiovascular aging, whereas their genetically determined favorable phenotypes have been associated with longevity. Telomere shortening is associated with increased cardiovascular aging through modulation of atherosclerotic disease, while it is also related with short life span. Delaying cardiovascular aging, through modifiable (e.g., diet, exercise), nonmodifiable (genes), and mixed modifiable/nonmodifiable factors (environment), may promote longevity, as this is suggested by experimental/clinical studies and reinforced by epidemiological studies in long-living populations.

**AIR POLLUTION.** Air pollution was estimated to account for 6% of global mortality burden in 2010 (117), and substantially increases the burden of respiratory and CV diseases. Inhaled air pollutants increase oxidative stress and induce inflammation (118). Moreover, air pollution increases arterial stiffness and wave reflections (119), and promotes endothelial dysfunction and atherosclerotic plaque formation, expansion, and vulnerability, whereas it may also facilitate platelet activation and aggregation (118). In the MESA Air Study (Multi-Ethnic Study of Atherosclerosis and Air Pollution), long-term exposure to air pollutants <2.5 μm in aerodynamic diameter ($PM_{2.5}$) was related to increased cardiovascular mortality, partially attributed to endothelial dysfunction given that short-term exposure to $PM_{2.5}$ was associated with decreased FMD and vasoconstriction (120). In addition, recent data support the notion that air pollution may accelerate vascular aging through telomere shortening (121) and modulation of DNA methylation (122). Importantly, a large U.S. study demonstrated that reduction in air pollution within a 20-year period in U.S. urban regions was associated with a significant increase in life expectancy (123).

**CLIMATE.** Climate and its measured variables also may have an impact on health and longevity. There is evidence between ambient temperature and cardiovascular mortality, suggesting that both cold and hot temperatures may affect cardiovascular mortality, although the effect of cold is stronger. Recently, data on the association of weather patterns and total mortality across 9 regions of England showed that people in regions with cold weather are more susceptible to CVD (124), a finding compatible with previous results from 15 European cities where low temperatures during the cold season were associated with increased CV and respiratory mortality, especially in subjects age >65 years (125). It is of note that in China, the highest

longevity rates were observed in coastal and southern regions of China, where the humidity is higher, the standard deviation of monthly temperature is lower, and the soil is enriched with selenium (126).

**GAMMA (γ) RADIATION.** Environmental conditions and geological composition of the Ikaria island may also contribute to the inhabitants' longevity, although such a hypothesis clearly requires further evidence to be confirmed. Data show that levels of gamma (γ) radiation are higher in the western and west-north part of the island compared with eastern Ikaria (127). Interestingly, according to data from the National Statistical Service of Greece, rate of persons age >90 years and survival rate across the past 50 years were higher in the western and west-north part of Ikaria compared with the eastern part. Moreover, evidence from the IKARIA study suggested that elderly participants living in places with higher gamma radiation had lower prevalence of obesity and higher antioxidant capacity (128).

The role of environmental radiation on cancer risk and mortality has been investigated in the past. In 1973, the U.S. Atomic Energy Commission had underlined the difference in cancer mortality between regions with different levels of radiation, as 6 states with the higher exposure to radiation exhibited 15% lower cancer mortality risk compared with the average national rate (129). This finding was reinforced in 1998, when it was shown that the 3 Rocky Mountain states had 3.2-fold higher annual radiation levels compared with the 3 Gulf Coast states, but cancer mortality was higher in the Gulf Coast states by 26% (130). The theory that has been proposed is that there may be a threshold, below which exposure to radiation could have a beneficial effect on human health due to stimulation of DNA repair mechanisms (131,132). Experimental studies have shown that low-level radiation before exposure to large radiation doses may protect from DNA damage, as it resulted in reduced chromosome aberrations and gene mutations, whereas other investigators reported an increase in life span of mice after very low dose continuous gamma irradiation (133).

Overall, the issue of the potential beneficial effect of low-dose gamma radiation remains unresolved, and future studies are warranted to elucidate its exact role on longevity.

## LONGEVITY: LESSONS FROM THE PAST

The most intriguing report regarding longevity comes from a Bishop almost 400 years before the identification of the "Blue Zones" (134). Joseph Georgirenes, Archbishop of Ikaria-Samos, in a book published in 1677 (**Figure 6**), described, for the first time, the unique phenomenon of longevity in Ikaria inhabitants, highlighting the role of the favorable environmental conditions, Mediterranean diet, exercise, and positive feelings: *"The most commendable thing of this island is their air and water, both so healthful that the people are very long lived, it being an ordinary thing to see persons in it of an 100 years of age, which is a great wonder, considering how hardly they live. Eating, there is not a piece of bread to be found in the island. A little before dinner, they take as much corn as will serve that meal. Their diet is poor, yet their bodies are strong and hardy and the people generally long lived. They live as they expect not to survive a day, being contented to satisfy the present necessities of nature. Thus, you have an account of a small island, the poorest and yet, the happiest of the whole Aegean Sea…"*

Long before the identification of the 'Blue Zones' and the contemporary epidemiological studies, Joseph Georgirenes describes factors that favor CV health and longevity, such as diet, exercise, and environmental conditions.

## CLINICAL IMPLICATIONS: FUTURE DIRECTIONS

Since 1930, where, for the first time, the beneficial effect of calorie restriction on life span in mice was demonstrated, the research on the impact of genetic, epigenetic, molecular, biochemical, and environmental factors on aging, is growing rapidly. Notably, most of this research is applied in model organisms and experimental animals, thus, extrapolation of the results to human longevity should be considered with caution. Nonetheless, among the molecular factors, telomere length emerges as the most appealing biomarker of cardiovascular aging, with potential causal relationship with atherosclerosis, although with a small effect size (135).

Although causality cannot be firmly established, a pathophysiological hub between cardiovascular aging and longevity, is clearly demonstrated (**Central Illustration**). The most important known pathophysiological mechanisms of atherosclerotic disease, such as oxidative stress, low-grade inflammation and insulin resistance are also mechanisms of aging. The beneficial effects of lifestyle measures, such as healthy diet and exercise, on longevity, underscore the role of these mechanisms. Research focus on cardiovascular genetics and the environmentally driven epigenetic modulations may aid on personalized cardiovascular therapeutic interventions that will promote longevity.

Long-living populations are the optimal substrate for such research.

## CONCLUSIONS

Longevity and cardiovascular aging are closely interrelated. Mechanisms that promote longevity, contribute also to slowing of CV aging. Future studies on the interaction between the underlying genetic and environmental factors may further explore the pathophysiological mechanisms and introduce novel interventions to healthy (CV) aging and longevity.

## AUTHOR DISCLOSURES

Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** aging, cardiovascular disease, longevity