Title

Impact of Aging on Cardiovascular Diseases: From Chronological Observation to Biological Insights: JACC Family Series.

Journal

JACC: Asia, 4(5)

Authors

Zhao, Dong
Wang, Jianan
Wang, Yibin
et al.

Publication Date

2024-05-01

DOI

10.1016/j.jacasi.2024.02.002

JACC: ASIA VOL. 4, NO. 5, 2024

JACC FAMILY SERIES

Impact of Aging on Cardiovascular Diseases

From Chronological Observation to Biological Insights: *JACC* Family Series

Dong Zhao, MD, PhD,[a,*] Yibin Wang, PhD,[b,*] Nathan D. Wong, PhD,[c] Jian'an Wang, MD, PhD[d]

ABSTRACT

Cardiovascular disease (CVD) has increasing challenges for human health with an increasingly aging population worldwide, imposing a significant obstacle to the goal of healthy aging. Rapid advancements in our understanding of biological aging process have shed new light on some important insights to aging-related diseases. Although numerous reviews delved into the mechanisms through which biological aging affects CVD and age-related diseases, most of these reviews relied heavily on research related to cellular and molecular processes often observed from animal experiments. Few reviews have provided insights that connect hypotheses regarding the biological aging process with the observed patterns of chronological aging-related impacts on CVD in human populations. The purpose of this review is to highlight some of the major questions in studies of aging-related CVD and provide our perspectives in the context of real-world patterns of CVD with multidimensional information and potential biological insights. (JACC: Asia 2024;4:345-358)

The 2023 World Health Organization (WHO) report noted a global decline of 27% in age-standardized mortality related to cardiovascular disease (CVD) between the years 2000 and 2019.[1] This substantial reduction in age-standardized CVD mortality underscores the success of prevention initiatives implemented in numerous countries. These initiatives have harnessed established knowledge regarding CVD risk factors, deployed effective interventions, and promoted the adherence to evidence-based practices within both clinical and broader population settings.

Despite these notable achievements, the actual burden of CVD, as measured by the number of CVD-related deaths, increased by 33%, whereas crude CVD mortality rose by 6% over the same period.[2] This increase can be primarily attributed to the substantial impact of demographic transition toward increasingly aged populations.[3-8] Globally, the total aged population defined as age ≥65 years will increase from 770.4 million in 2022 to 1.58 billion in 2050, representing an increase from 9.7% of the global population to 16.4%. This dramatic increase in the size and proportion of the aged population has been observed and is projected to further aggravate in all regions globally (**Figure 1**).[3,4] Importantly, the reductions in CVD burden achieved through prevention efforts has been—and will be—further offset by the impact of the increase on the aged population.[5-8]

For a long time, aging has been regarded as an unmodifiable CVD risk factor—akin to sex—at both individual and population levels. Therefore, although

From the [a]Capital Medical University Beijing Anzhen Hospital, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China; [b]Duke-NUS Medical School and National Heart Center of Singapore, Singapore; [c]Division of Cardiology, University of California, Irvine, California, USA; and the [d]Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, Zhejiang, China. *Drs Zhao and Wang are co-first authors.
Latha Palaniappan, MD, served as Guest Associate Editor of this paper. William F. Fearon, MD, served as Guest Editor-in-Chief of this paper.

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 October 2, 2023; revised manuscript received February 9, 2024, accepted February 12, 2024.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2024.02.002

ABBREVIATIONS AND ACRONYMS

AAA = abdominal aortic aneurysm

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CAS = carotid artery stenosis

CVD = cardiovascular disease

FMD = flow-mediated vasodilation

GBD = global burden of disease

IMT = intima-media thickness

NCD = noncommunicable disease

PAD = peripheral artery disease

PWV = pulse-wave velocity

SBP = systolic blood pressure

SDI = socio-demographic index

TC = total cholesterol

WHO = World Health Organization

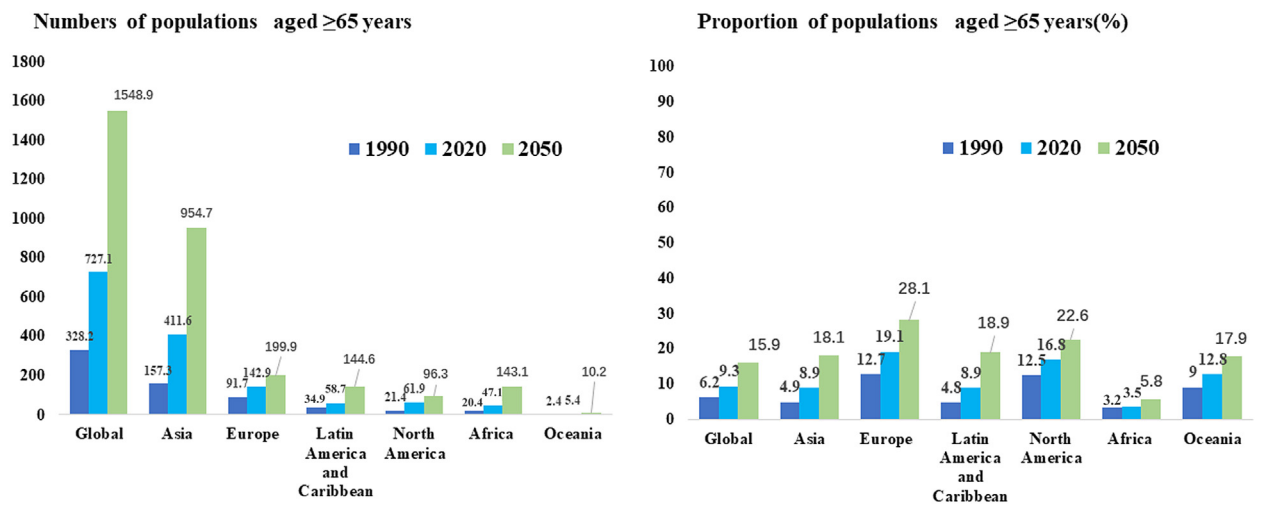
age is an essential factor considered in all available CVD risk-assessment tools used routinely in clinical practice, the recommendations specifically made on how to lower aging-related CVD risk have been very limited as part of the prevention guidelines for CVD.[9-11] Almost all publications regarding CVD burden at the population level use only age-standardized rates and the CVD burden caused by the impact of aging is largely overlooked.[11-14] This leads to a pressing question: Can we confront these challenges and diminish or delay the residual risk of CVD associated with aging at both the population and individual levels? Obviously, this inquiry extends beyond CVD and encompasses all age-related diseases.

Rapid advancements in our understanding of aging have shed new light on some important insights to the process. First, although chronological age—as defined by time from birth—is an unmodifiable parameter for individuals or a given population, biological age (as loosely defined by the biological state of an individual along the entire ageing continuum) may be altered by both intrinsic (genetic makeup) and extrinsic (lifestyle, risk exposure) factors. Although the chronological aging of a population is clearly an important parameter for current CVD burden, the rate of biological aging (also termed "age acceleration" or "age deviation") is an even more important determinant to the disease trend. Consequently, uncovering and modifying the underlying drivers of biological aging and aging acceleration would hold significant potential for clinical application. This ongoing progress continually provides new insights and opportunities for the prevention of CVD and noncommunicable diseases (NCDs) within the context of the impact of biological aging.[15-17]

Although numerous reviews have delved into the mechanisms through which biological aging affects CVD and age-related diseases, most of these reviews heavily rely on research related to cellular and molecular processes often observed from animal experiments.[17-19] Few reviews have provided insights that connect hypotheses regarding the biological aging process with the patterns of chronological aging-related effects on CVD in human populations.

To bridge this gap, this review aims to pose critical translational questions derived from the studies on biological aging, relate these questions to the tangible patterns of chronological aging-related effects on CVD, and provide valuable insights that can stimulate future research endeavors and expedite the translation of biological aging hypotheses. The content of this review draws upon a comprehensive review of the literature and an analysis of the available age-specific data from the Global Burden of Disease (GBD) database. This data source is an open database of the GBD study accessible through the Global Health

FIGURE 1 Increasing Aged Populations Around the World From 1990 to 2050



Increasing sizes and proportions of populations aged ≥65 years from 1990 to 2050 in global and 6 world regions based on published data from the World Health Organization and World Bank.[3,4]

Data Exchange at The Institute for Health Metrics and Evaluation. The details of the relevant methodology and quality assessment are available on the published papers or on the GBD study website.[2,20]

DEFINITIONS OR CONCEPTS OF CHRONOLOGICAL AND BIOLOGICAL AGE AND AGING

Chronological age in individuals is defined as the time that has passed since birth. This measure increases unidirectionally and irreversibly throughout a person's lifespan. The concept of chronological aging is further defined by arbitrary criteria. According to the updated criteria of the WHO, individuals are considered aged when they reach the age of 65 years or older. At the population level, a population is classified as an aging population when the proportion of individuals aged 65 years and above reaches 7% and as an aged population when that proportion reaches 14%.[21]

The concept of biological age pertains to the functional state of the individual, often measured by physiological functions of cells, tissues, and organs that shape and sustain the essence of life.

A definition of biological aging refers to the process of comprehensive biological degeneration of structures and functions of human body in aging people. At functional levels, biological aging is characterized by a progressive decline in physiological ability to meet demands and loss of resilience and regenerative capacity. At the mechanistic level, numerous hypotheses for an intrinsic biological process have been proposed, including accumulation of damage at DNA, protein, and organelle levels; loss of reparative machinery; and diminished renewal at molecular and cellular levels.[22-26] Although the concept of biological aging is straightforward, the science of determining biological aging process accurately—especially the intrinsic biological process in the clinical setting—proves to be very challenging and problematic. Much of the focus in aging research is to find ways to mitigate or delay the accumulation of chronologically related damages by reducing risk exposures while boosting reparative and regenerative activities. Ultimately, the goal of biological aging research is to slow aging acceleration or reverse biological aging and extend the period of healthy living. In recent decades, a number of biomarkers have been developed for humans, including telomere length and more robustly DNA methylation pattern-based epigenetic clock.[25-27] The further development of these tools should allow investigators to characterize the pace and the mechanisms of biological aging process unambiguously as well as search mitigation strategies that can affect the biological aging process. At present, our discussions on both biological age and rate of biological aging in humans remain primarily at a conceptual level, and much research is needed to translate this concept into our daily clinical practices with specific guidelines.

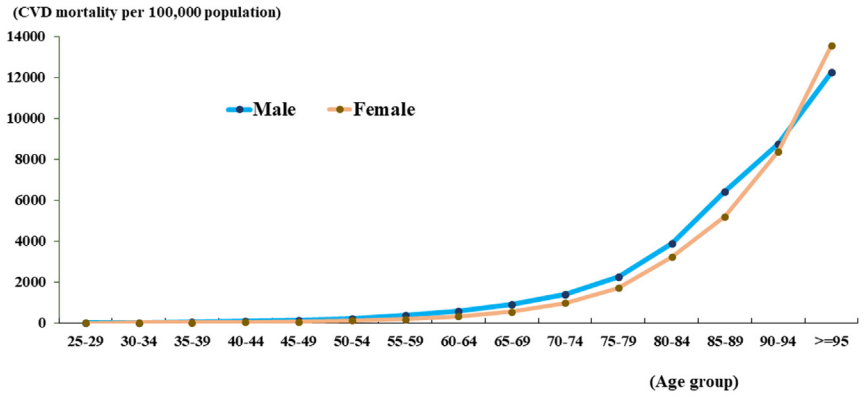
As part of growing awareness of biological aging, concepts such as "vessel aging" or "cardiovascular aging" in people have also gained traction in recent years. In several studies examining the impact of aging, parameters obtained from direct measurement of heart and vascular structures or functions were used as either specific outcomes for association analysis, or collective predictors of future CVD risk.[28,29] Several cardiac and vascular functional or structural parameters are featured in aging studies such as pulse-wave velocity (PWV), arterial intima-media thickness (IMT) in carotid arteries, coronary artery calcification (CAC), and flow-mediated vasodilation (FMD). The rationale behind their selection is that these parameters can serve as more quantifiable phenotypes to gauge the aging process for the cardiovascular system, and it is also governed by the underlying biological aging process.[30-33] However, there is a lack of integrated parameters or scores to measure cardiovascular age and pace of biological aging based on aging specific biomarkers, structural, and functional measurements that can be applicable in clinical practice.

QUESTIONS FOR BIOLOGICAL AGING-RELATED IMPACT ON CVD

In 2020, Cohen et al[34] reported the results of a survey conducted during a symposium on biology of aging, involving the participants' perspectives on key questions related to biological aging studies. The survey revealed a significant lack of consensus and marked disagreement among experts, even on some of the most fundamental questions within the field. These contentious issues included debates about when aging begins and whether aging is a programmed process or not.

Two of the possible reasons for the lack of consensus in biological aging studies are insufficient evidence for a significant impact of these biological aging processes in humans and lack of objective criteria for "aging" in humans except for chronological age. In our opinion, the following questions can link the characteristics of CVD, one of the most significant chronological aging-related diseases, to the hypotheses of biological aging process in CVD. 1) Although the criteria of measurable biological age and

FIGURE 2 Global Age-Specific CVD Mortality Rates in 2019



Global age-specific CVD mortality rates in 2019 illustrate the association between aging and CVD mortality through the exponential curve of age-specific CVD mortality from age 25 years to age ≥95 years of the world population.[2] CVD = cardiovascular disease.

aging are not available in humans, what are the patterns and magnitude of chronological age-related manifestation of CVD that imply the importance of the underlying biological aging process in CVD? 2) What are the findings in long-term cohort studies on the effects of multiple CVD risk factors that can provide insights to the possible independent effects of the hypothetical intrinsic biological aging process vs the effects of the extrinsic factors in shaping the process of biological aging? 3) Can we find in certain chronological age when the effects of CVD risk, potentially stemming from the intrinsic biological aging process, become irreversible? 4) Do the biological aging processes have unique impact on CVD that differ from other aging-related diseases such as cancer?

WHAT ARE THE PATTERNS OF THE AGING-RELATED IMPACT ON CVD IN THE HUMAN POPULATION?

PATTERNS OF CHRONOLOGICAL AGING-RELATED IMPACT ON CVD MORTALITY. In a survey addressing specific inquiries within the field of aging research, 76% of the participants engaged in aging research agreed that mortality rates or survival curves can often serve as a reasonable proxy for assessing aging at organismal level.[34] Among the major risk factors for CVD, chronological age stands out as a potent indicator. At present, we lack a specific pattern of biological aging-related CVD deaths in humans. However, the association between chronological age and CVD mortality patterns can serve as a foundational reference for understanding the potential effect of biological aging. The global chronological age-specific CVD mortality rate can be viewed as the average probability of experiencing a CVD event within a specific age or age group at any given time in the human population. However, many publications focusing on the epidemiologic aspects of CVD mortality at a global scale often offer limited insights into age-specific CVD mortality patterns.

To address this limitation and provide updated information, we conducted an analysis of age-specific mortality data from the GBD database. This comprehensive database supplies mortality data for all causes across various age groups, ranging from newborns to individuals aged 95 and older, spanning the years from 1990 to 2019.[2] **Figure 2** illustrates a fundamental pattern of global age-specific CVD mortality rates for both men and women in 2019, focusing on populations aged 25 to ≥95 years in 5-year intervals. CVD mortality rates for both men and women consistently increased with advancing age, following an exponential curve that steepened as age increased. This exponential pattern indicates a more rapid rise in CVD mortality rates with older age.

The mean doubling time for CVD mortality was 7.2 years in men and 6.5 years in women. To put this into perspective, the observed CVD mortality rates in the population aged 65 to 69 years were 61 and 67 times higher than those in the 25 to 29 years age group for men and women, respectively. Furthermore, in the age of 85 to 89 population, the CVD mortality rates for

men and women were a striking 441 and 630 times higher, respectively, than in the 25- to 29-year age group. This steep and dramatic increase in CVD mortality with advanced age underscores that CVD, as a constellation of multiple diseases is a profoundly aging-related disease. A potential limitation is that cardiovascular death is sometimes given as a cause when there are no other obvious causes, making it difficult to get precise quantitative estimates regarding the contribution of biological aging to cardiovascular morbidity and mortality; however, this should not dramatically affect any findings regarding trends in cardiovascular mortality.

PATTERNS OF AGING-RELATED PREVALENCE OF VASCULAR DISEASE IN DIFFERENT ARTERIAL TERRITORIES. Significant evidence concerning the impact of aging can be derived from studies involving direct measurements in various arterial territories. A large-scale study involving more than 3.6 million participants in the United States who completed medical and lifestyle questionnaires—as well as screening for peripheral artery disease (PAD)—using ankle-brachial index (ABI) (with PAD defined as an ABI <0.9) and ultrasound imaging (with carotid artery stenosis [CAS] defined as $\geq 50\%$ and abdominal aortic aneurysm was based on an aortic diameter of 3 cm or more).[35] The prevalence of PAD and CAS exhibited an exponential increase with advanced age, spanning from ages 40 to 50 years and 91 to 100 years, for both men and women, irrespective of whether individuals were symptomatic or asymptomatic.

Several large-scale autopsy studies conducted in different countries and among diverse ethnic groups have consistently revealed that atherosclerosis becomes more prevalent as individuals age, affecting various arterial territories.[36-38] One notable study conducted in China during the 1980s, a period when China had a lower socio-demographic index (SDI) level and lower risk factors for atherosclerotic cardiovascular disease (ASCVD), analyzed 7,159 autopsy cases, spanning from infants to people above the age of 90 years. This study observed a substantial increase in the proportion of atherosclerosis and stenosis in coronary arteries with advancing age. Specifically, the prevalence of atherosclerosis was 58% in people aged 40 to 49 years, 87% in those aged 60 to 69 years, and reached 100% in those above the age of 90 years. Importantly, these autopsy studies not only underscore the impact of aging on atherosclerosis but also consistently demonstrate that atherosclerotic changes can be found in individuals at very early stages of life, with a 10% prevalence noted among those aged only 10 to 19 years.[36]

These consistent findings—regarding the impact of chronological aging on CVD mortality and vascular diseases across various arteries, spanning different time periods, countries, and ethnic groups, regardless of socioeconomic and level of major modifiable risk factors—may imply on the pattern and magnitude of CVD aggravation driven by biological aging process and underscore the critical importance of biological aging research in elucidating the underlying mechanisms of this phenomenon.

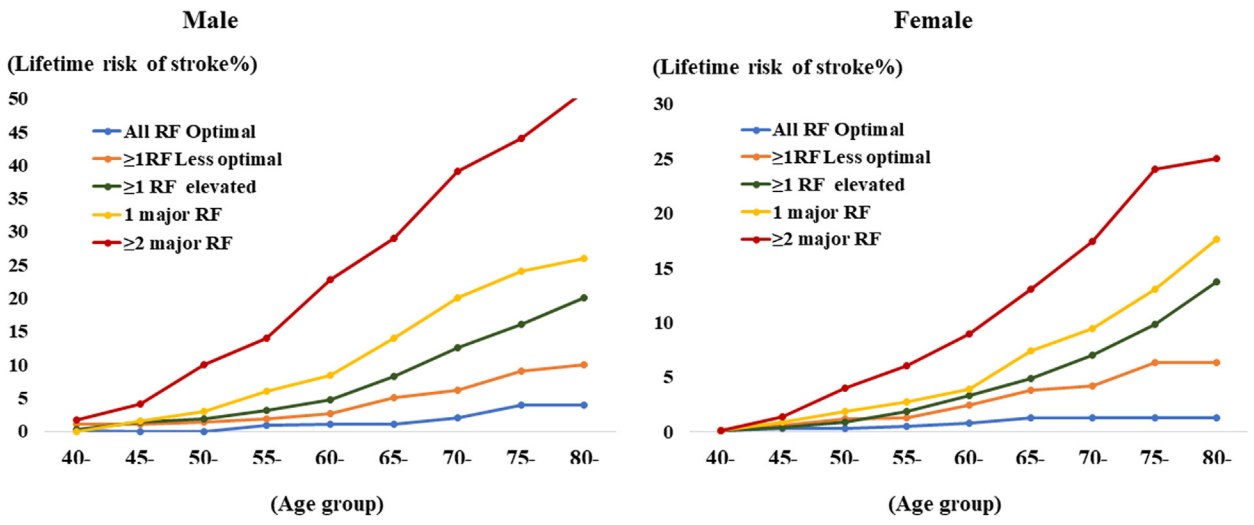
WHAT IS THE MAGNITUDE OF INDEPENDENT AGING-RELATED IMPACT ON CVD RISK?

One of the explanations for the exponential increase in CVD mortality risk associated with advancing age is predominantly caused by prolonged exposure to modifiable CVD risk factors—including high systolic blood pressure (SBP), elevated total cholesterol (TC) or low-density lipoprotein-cholesterol (LDL-C) levels, smoking, diabetes, and obesity—in the aging population. This leads us to ponder the magnitude of impact potentially stemming from the intrinsic biological aging process such as natural senescence of cells, proteostasis, or other molecular processes, as well as their interactions with the extrinsic factors associated with the heightened CVD risk. These questions become pivotal in estimating the extent to which the residual risk resulting from the intrinsic aging process may be irreversible, thus determining the ultimate lifespan of the cardiovascular system. With such insight, we will be able to evaluate the potential effect of additional new interventions on the specific residual CVD risk associated with aging. Addressing these questions is crucial for developing effective strategies to mitigate age-related CVD risk and to promote healthier aging.

INDEPENDENT IMPACT AND INTERACTION OF AGING ON LIFETIME CVD RISK. Studying lifetime risk for CVD provides compelling evidence for the independent effect of aging, which may reflect the potential impact of the hypothetical intrinsic biological aging process and the interactions between this aging process and major CVD risk factors such as blood pressure, lipids, smoking status, and diabetes status.[22-26,39-42]

A meta-analysis of 18 cohort studies in the United States investigated lifetime risks of CVD across the age spectrum. The curve depicting lifetime CVD risk as individuals age at 50 with optimal level of risk factors showed the potential independent impact of the biological aging process and the interplay

FIGURE 3 Lifetime Risk of Stroke in Individuals With Different Risk-Factor Profiles



Potential impact of the hypothetical intrinsic biological aging process on risk of major types of CVD and the interactions between the hypothetical intrinsic biological aging and major CVD risk factors such as blood pressure, lipids, smoking status, and diabetes status. Reprinted with permission from Wang et al.[40] Abbreviations as in Figure 2.

between the biological aging process and the presence and extent of risk factors.[39] Similar patterns for lifetime CVD risk have also been reported in other studies globally.[40-42]

As illustrated in Figure 3, the independent impact of aging-related effects on lifetime stroke risk for individuals aged 40 years or greater was demonstrated in a lifetime study of stroke in China. When all risk factors were at optimal levels, the risk of stroke remained low or raised slightly from age 40 to 80 years in men and women. The aging-related impact—which may stem from the hypothetical intrinsic biological aging process—on lifetime stroke risk was significantly lower compared with individuals with elevated risk factors. The gradual increases in risk during the aging process were observed at each level of risk-factor profile from not optimal, ≥1 elevated risk factors, 1 major risk factor, to ≥2 major risk factors. This may reflect not only the additive impact of risk factors to the basic effect of the hypothetical intrinsic biological aging but also the synergistic effects of risk factors interacting with the intrinsic biological aging.[40]

INDEPENDENT IMPACT AND INTERACTION OF AGING IN RISK-ASSESSMENT MODEL OF ASCVD. Data from long-term cohort studies, which assessed individuals with diverse risk-factor profiles, have offered more precise quantification of the independent impact of age and aging and the interactions between aging and other risk factors.[43-46] In a model developed by the WHO CVD Risk Chart Working Group, which drew data from 80 cohort studies involving approximately 1 million individuals without histories of CVD at baseline from across the globe, it was observed that for each 5-year increase in age from the baseline age of 40 years, the 10-year risk of fatal and nonfatal acute myocardial infarction and coronary heart disease death increased independently by 43% (HR: 1.43 [95% CI: 1.40-1.47]) in men and 67% (HR: 1.67 [95% CI: 1.60-1.73]) in women.[43] In comparison, the corresponding independent effects resulting from a 20-mm Hg increase in SBP were 30% (HR: 1.30 [95% CI: 1.28-1.33]) in men and 37% (HR: 1.37 [95% CI: 1.33-1.42]) in women. When assessing the risk of stroke, it was found that for each 5-year increase in age from the baseline age of 40 years, the 10-year risk of fatal and nonfatal stroke increased independently by 64% (HR: 1.64 [95% CI: 1.58-1.70]) in men and 70% (HR: 1.70 [95% CI: 1.58-1.70]) in women.

However, the reported increase in HRs of independent age-related CVD risk in each 5-year increment of age from 40 years in men and women is less consistent with the finding of the lower independent impact of aging on lifetime CVD risk when all risk factors were at optimal levels. One possible explanation is that the reported HRs of independent age-

related CVD risk was mean HRs derived from Cox regression models based on presumed linear associations between age and CVD risk when it was actually a nonlinear association. The analyses of interaction between age and major risk factors for CVD outcomes suggest that, as individuals grow older, the general influence from aging process becomes more pronounced in both groups with higher or relatively lower level of risk factors. The independent effect from elevated SBP, TC, diabetes, and smoking on CVD outcomes are actually diminishing relatively as individuals age.[43]

NONLINEAR IMPACT OF AGING-RELATED ON PREVALENCE OF VASCULAR DISEASE IN DIFFERENT ARTERIAL TERRITORIES. In a large-scale study in the United States, involving more than 3.6 million participants who completed medical and lifestyle questionnaires, individuals were assessed through screening ankle brachial indices for PAD and underwent ultrasound imaging to evaluate carotid artery CAS and abdominal aortic aneurysms (AAAs).[35] A nonlinear effect of aging on vascular diseases was identified. When people at the 40- to 50-year age group were taken as reference, there were notably elevated risks of vascular disease in different arterial territories. For example, compared with those aged 40 to 50 years, the adjusted OR for PAD was 5 times greater at age 71 to 80 years and 12 and 27 times greater at ages 81 to 90 years and 91 to 100 years, respectively.[35]

In summary, there were several implications for potential impact of biological aging from the findings here. First, the patterns of independent effect from aging in lifetime risk studies imply that the potential impact of the hypothetical intrinsic biological aging on the risk of CVD events could remain relatively low and retarded until 75, or even 80, years of age if all other major risk factors were kept at optimal levels. Second, the impact of aging may be augmented substantially when external risk factors are elevated, implying that the elevated modifiable risk factors could accelerate the hypothetical intrinsic biological aging process significantly in a dose-response pattern, which, in turn, may also be the driver of elevated modifiable CVD risk factors such as blood pressure, lipids, and chronic inflammation. Third, the potential effects from the intrinsic biological aging process may increase nonlinearly with aging in all individuals, becoming more predominant with dramatically elevated risk of CVD in older persons. We have to acknowledge the potential contribution of newly discovered environmental or acquired CVD risk factors that have emerged more recently than what is currently available in survey data and also that the impact of unknown extrinsic risk factors are not considered in this argument.

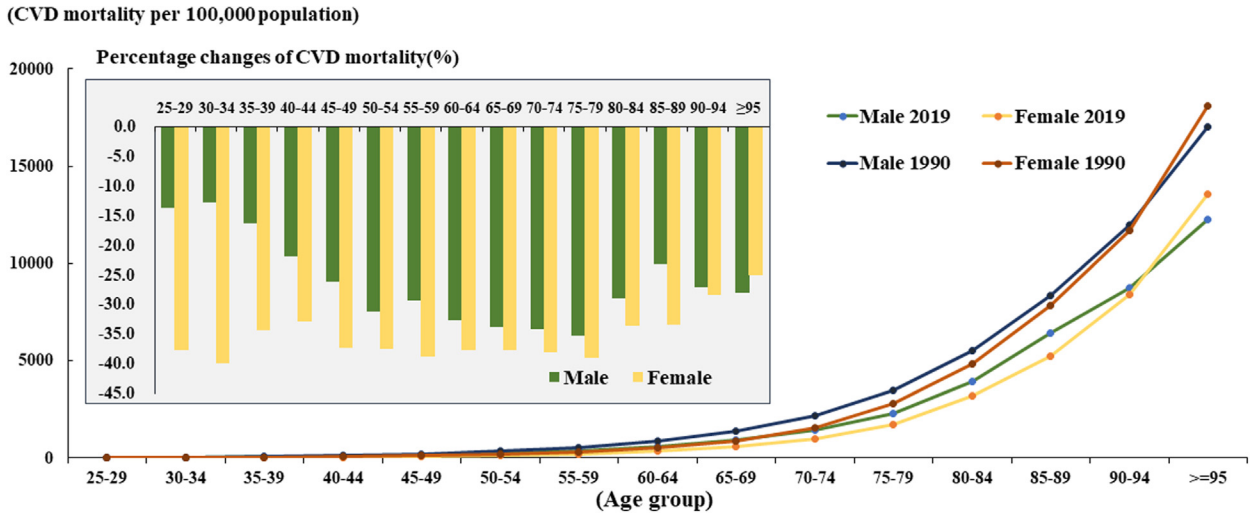
IS THE AGING-RELATED IMPACT ON CVD RISK MODIFIABLE?

CHANGES OF AGE-RELATED IMPACT ON CVD MORTALITY ACROSS DIFFERENT TIME. It can be inferred that if the notable surge in CVD mortality up to a certain age point would be driven primarily by the programmed and hard-to-reverse biological aging process, then CVD mortality beyond this age might exhibit relatively fewer fluctuations, even over extended periods and across countries with significant differences in socioeconomic levels. Adams and White[22] provided not only a reasonable definition of biological aging but also hypothesized a pathway linking socioeconomic status, risk factors, and genetic determinants for the rate of biological aging and health status in their paper entitled “Biological Aging” published in 2004. However, there is no previous evidence to support this proposed paradigm in large population studies for CVD.

Therefore, we compared the age-specific CVD mortality rates in 2019 with those in 1990. Although data from both 1990 and 2019 saw CVD mortality rates increase exponentially with chronological age, there was a significant decrease in CVD mortality from 1990 to 2019 for each age group from 25 to ≥95 years (**Figure 4**). In men, the most substantial decrease in CVD mortality occurred in the 75- to 79-year age group, with a 35% decline from 1990 to 2019. Moreover, the magnitudes of decline in the 90- to 94- and ≥95-year age groups were larger than that in the 40- to 44-age group. In women, the magnitude of decrease in CVD mortality from 1990 to 2019 exceeded that in men across all age groups except for those aged 95 years, in which the decline was notable as well. This reduction ranged from 25% to 40% across the entire age spectrum (**Figure 4**). Remarkably, in 2019, it took approximately 5 additional years to reach a mortality rate similar to that of 1990 across age groups from 25 to ≥95 years, both in men and women. Notably, there was no distinct chronological age point at which a relatively stable mortality rate was observed over the 3-decade period.

CHANGES OF AGE-RELATED IMPACT ON CVD MORTALITY ACROSS POPULATIONS WITH DIFFERENT SDI LEVELS. In 1990, it was evident that countries with a low SDI had significantly higher CVD mortality rates than those with a high SDI,[2] but this difference was observed only before the age of 75 years in men and before the age of 80 years in women. But, in 2019, we

FIGURE 4 Decreasing Age-Specific CVD Mortality Rates From 1990 to 2019



Decrease in age-specific CVD mortality rate from 1990 to 2019 across all age groups from 25 to ≥95 years, both in men and women.[2] Abbreviations as in Figure 2.

observed that these differences in CVD mortality between low and high SDI countries not only persisted but also intensified. These disparities extended to all age groups except those aged ≥95 years, encompassing both men and women.

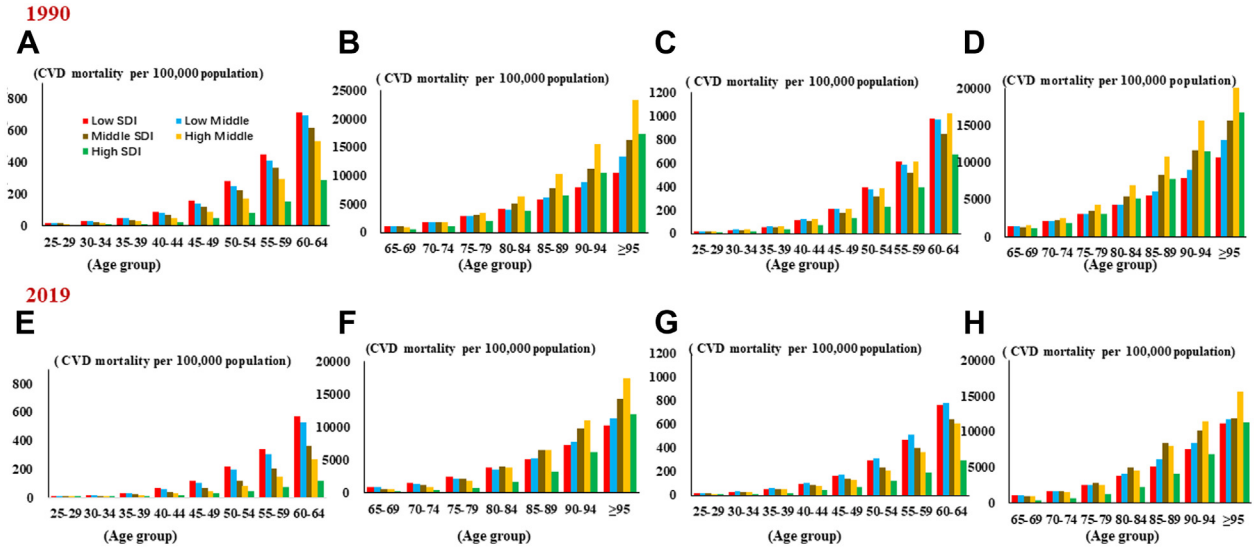
High-SDI countries enjoyed delays of 10 to 20 years in reaching similar CVD mortality rates as low-SDI countries, with the larger delay in women and a slightly smaller delay in men, all before the age of ≥95 years (Figure 5). From 1990 to 2019, there was a notable decrease in CVD mortality across all age groups in countries with high SDIs, ranging from 32% to 62% in men and 31% to 64% in women (Figure 6). Even in countries with low SDIs, significant reductions in CVD mortality were observed across age groups, especially before the ages of 75 to 79 years, although the magnitude of decline was somewhat lower compared with countries with high SDIs.[2]

The significant decrease in CVD mortality across all chronological age groups in only 3 decades, even across countries with varying SDI levels, suggests that the effect of the biological aging process on CVD can be modified, even in individuals aged ≥95 years, using current known preventive strategies. Throughout our analysis, we did not identify any specific age point, from 25 to ≥95 years, at which CVD mortality remained relatively unchanged, indicating that there is significant potential to further reduce CVD mortality to a level that delays by 10 to 20 years compared with countries with lower SDI levels as they undergo socioeconomic development.

The decline in CVD mortality across all age groups, and notably lower mortality among the elderly population in countries with high SDIs, potentially can be attributed to a combination of factors and the interactions among them, including the delayed or alleviated effect from both the biological aging process and improved management of modifiable risk factors such as therapies for lipids (eg, statins); blood pressure; and diabetes as well as the influence of improved sanitation, nutrition, living conditions, and medical care of patients with CVD such as thrombolytic therapy or angioplasty as socioeconomic development. Consequently, the biological aging process in humans does not appear to be entirely irreversibly programmed. The decline in CVD mortality observed from 1990 to 2019 occurred not only in the young and middle-aged population but also in the elderly, further implying that the impact of biological aging on CVD may be modifiable even in very old populations. It implies an optimistic expectation for natural lifespan in humans.

Particularly intriguing is to understand how the underlying biological aging process has been modified in the last 30 years, especially in countries that have witnessed the most substantial decrease in CVD mortality among the elderly population, as these insights could offer valuable strategies for other nations.

FIGURE 5 Age-Specific CVD Mortality by Time and SDI



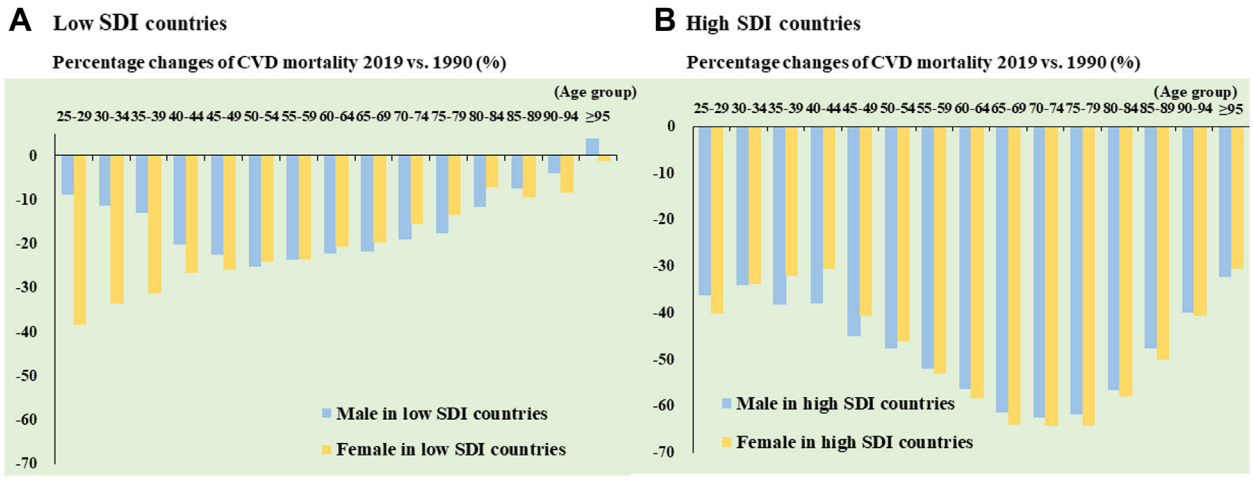
Differences in age-specific CVD mortality rates and changes in women and men among countries with different SDI levels (low, low middle, middle, high middle, and high) in 1990 and 2019.[2] (A) women ages 25 to 64 years in 1990; (B) women ages 65 to ≥95 years in 1990; (C) men ages 25 to 64 in 1990; (D) men ages 65 to ≥95 years in 1990; (E) women ages 25 to 64 years in 2019; (F) women ages 65 to ≥95 years in 2019; (G) men ages 25 to 64 in 2019; (H) men ages 65 to ≥95 years in 2019. SDI = Socio-demographic Index; other abbreviations as in Figure 2.

IS THE PATTERN OF AGING-RELATED EFFECTS FOR CVD SIMILAR FOR CANCER?

The biological aging process may serve as the basis for the development of multiple age-related diseases, given the increasing prevalence of multimorbidity in the aging population. In fact, both CVD and cancer have many common risk factors and been identified among the top 25 conditions contributing to multimorbidity, particularly in low- and middle-income countries.[47-49] It is reasonable to infer that new intervention strategies targeting key pathways of biological aging have the potential to prevent multiple age-related diseases. Notably, immunosenescence is considered a primary underlying cause of the increasing proinflammatory status in aging and aging-related diseases, particularly in CVD and cancer.[50,51] Based on this hypothesis, one might anticipate that, as individuals age, both CVD and cancer could exhibit similar patterns in age-specific mortality. There could even be an assumption that cancer might surpass CVD in terms of mortality rates among the super-aging population.

DIFFERENCES IN PATTERNS OF AGE-RELATED CVD MORALITY AND CANCER MORTALITY. However, several key differences in the patterns of the impact of chronological age between CVD and cancer can be observed. First, CVD exhibits a surged increase from ages 25 to ≥95 years in an exponential pattern. However, for cancer mortality, a sharper exponential increase is only seen from ages 25 to 29 years to ages 60 to 64 years, after which it significantly slows down among individuals aged 65 years and older, both in men and women. Across all age groups, CVD mortality remains higher than cancer mortality, with differences ranging from 1.5 to 3.7 times higher in men. In women, CVD mortality is initially lower than cancer mortality before age 60 years but reverses after age 60 years, with CVD mortality being 5.3 times and 6.2 times that of cancer mortality in individuals aged 90 to 94 years and ≥95 years, respectively (Figure 7). Next, women exhibit cancer mortality rates comparable with men from ages 25 to 49 years. However, starting from age 50 years, which typically coincides with the onset of menopause, women demonstrate a 10-year delay in reaching a similar level of cancer mortality rates compared with men. This pattern persists until the age bracket of 90 to 94 years (Figure 7). Finally, the patterns of the increasing rate of age-specific cancer mortality, as indicated by the sequential growth ratios per 5-year increase from ages 25 to ≥95 years, differ significantly from those of CVD (Figure 8). For cancer, the increase rates slow down

FIGURE 6 Decline in Rates of Age-Specific Cardiovascular Disease Mortality by SDI



Decreases in age-specific CVD mortality rate among countries with different SDI levels (low, low middle, middle, high middle, and high) from1990 to 2019.[2] (A) Countries with low SDI levels; (B) countries with high SDI levels. Abbreviations as in Figures 2 and 5.

after the age 50 to 54 years in both men and women. In contrast, CVD exhibits a much stronger aging-related pattern, with higher increase rates persisting until age 80 years, especially in women.

CHANGES OF AGE-RELATED IMPACT ON CANCER MORTALITY ACROSS DIFFERENT TIME AND POPULATIONS. When comparing cancer mortality rates in 2019 with those in 1990, a decline in cancer mortality is observed before the age of 85 years, with reductions ranging from 5% to 23% in women and 5% to 31% in men across the age groups of 25 to 29 years and 80 to 84 years. Notably, in countries with high SDIs, cancer mortality is considerably higher than in countries with low SDI levels, starting after age 60 years in women and age 50 years in men. Moreover, countries with high SDIs have witnessed much larger declines in cancer mortality from 1990 to 2019.

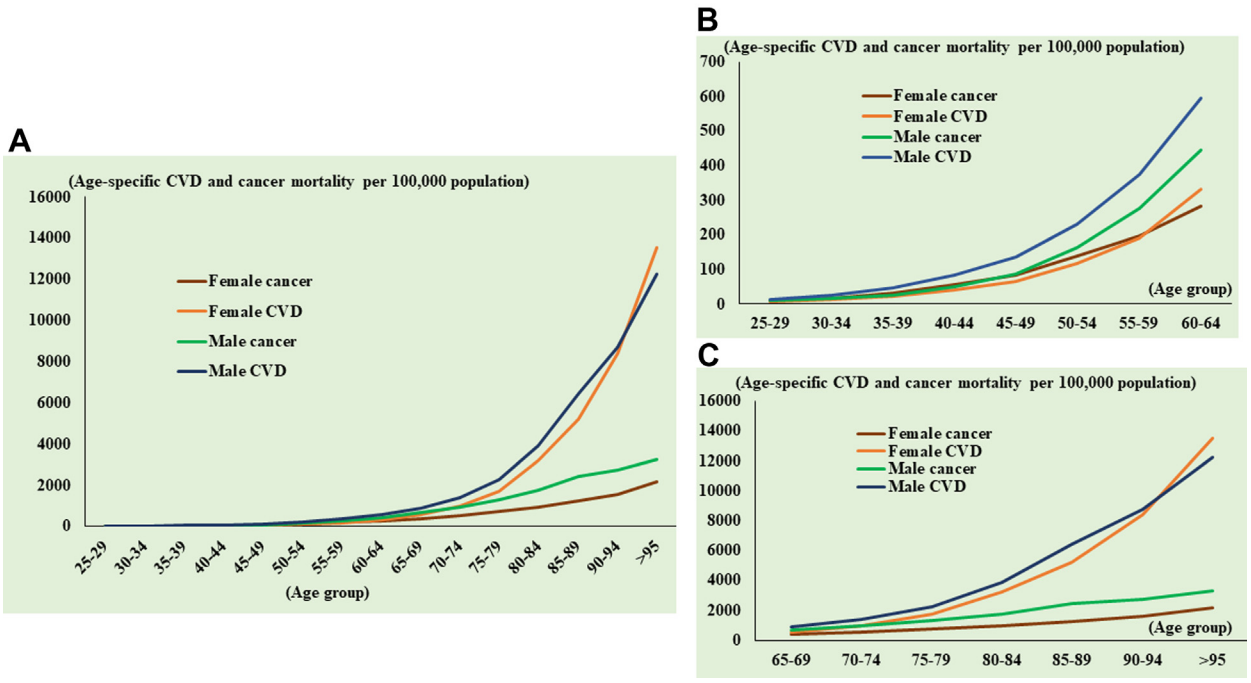
These distinct patterns of the effect of chronological aging between CVD and cancer may suggest different mechanisms or effects of the biological aging process on different age-related diseases. It is possible that different organs or systems have unique hallmarks and "clocks" in the aging process. These findings lead to questions such as "Why are age-specific CVD mortality rates significantly higher than cancer mortality, especially as individuals age?" "Why do women have lower cancer mortality rates than men after the age of 50 years, despite both men and women experiencing a substantial decline in immunologic function and metabolic health?"

CONCLUSIONS

Focusing on 4 critical translational questions derived from the study of biological aging, this review provides some insights that can stimulate future research endeavors and expedite the translation of the knowledge of biological aging from hypotheses to interventional strategies against harmful effects from aging in CVD prevention practice.

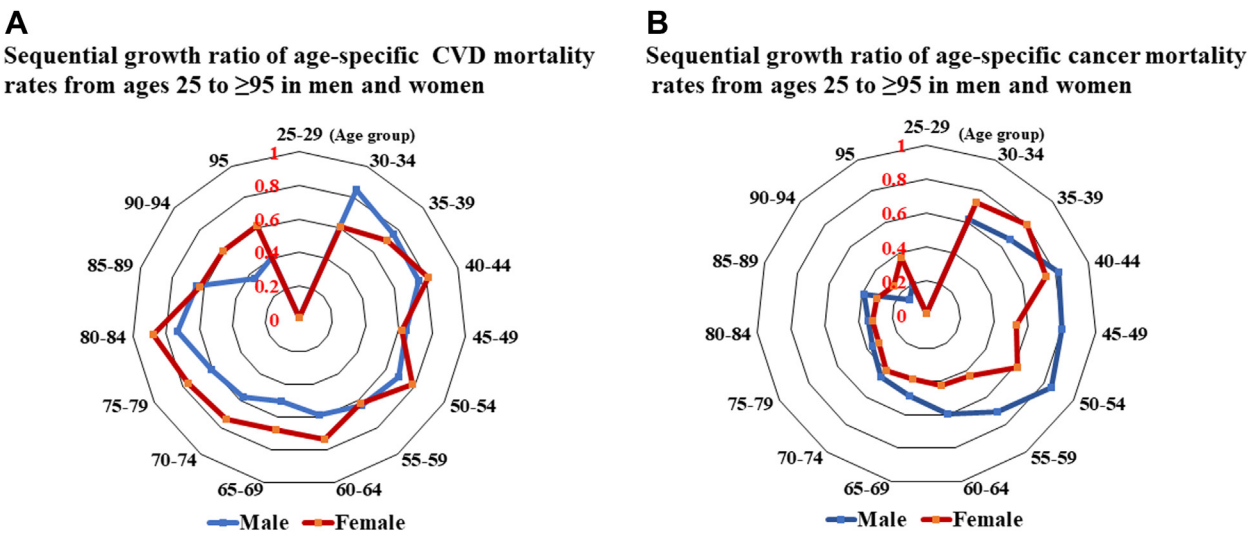
Several perspectives from this review are particularly noteworthy. First, the dramatic impact of chronological aging on CVD mortality and vascular diseases across various arteries can be considered as a mirrored estimation of the overall pattern and magnitude of CVD aggravation driven by the underlying biological aging process in humans. Second, although the intrinsic biological aging itself may play important role as a background driver of aging-related CVD risk, the overall contribution of biological aging process should encompass a synergistic effect of modifiable CVD risk factors (known and unknown) interacting with the intrinsic biological aging process. And the synergistic effect is very likely to be modifiable, influenced by socioeconomic development levels. Therefore, early interventions targeted to improving the control of risk factors and socioeconomic disparities will yield significant benefits in reducing adverse CVD outcomes over the lifespan (Central Illustration). Third, the distinct patterns of chronological aging effects between CVD and cancer may suggest different mechanisms or effects of the biological aging process on different age-related diseases. It is possible that

FIGURE 7 **Comparison of Age-Specific CVD and Cancer Mortality in 2019**



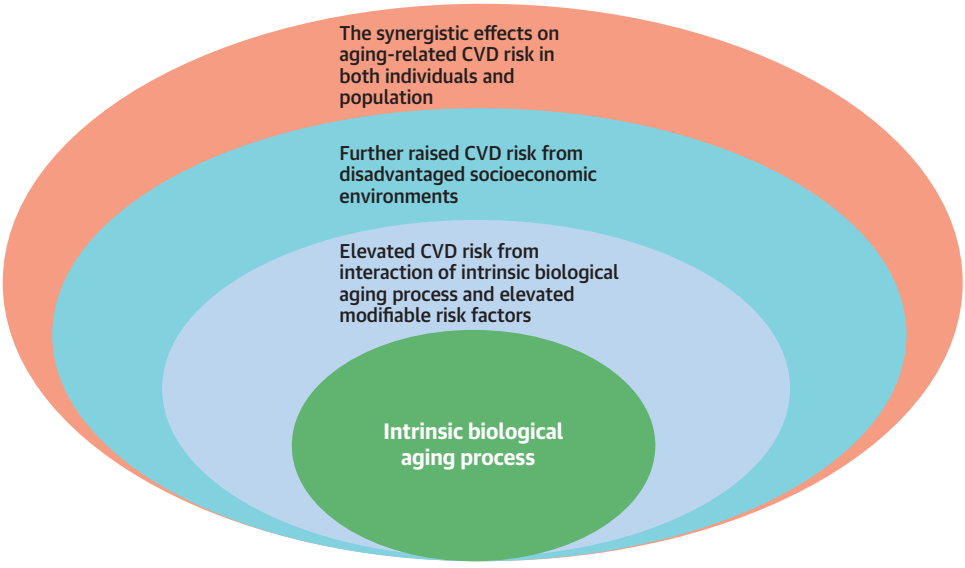
Patterns of age-specific CVD mortality and age-specific cancer mortality.[2] (A) Age-specific CVD mortality and cancer mortality from age 25 to 95 years; (B) age-specific CVD mortality and cancer mortality from age 25 to 64 years; and (C) age-specific CVD mortality and cancer mortality from age 65 to ≥95 years. Abbreviations as in Figure 2.

FIGURE 8 **Sequential Growth Ratios of Age-Specific CVD and Cancer Mortality Rates**



Gender-specific acceleration patterns CVD and cancer mortality as per 5 years' increase from ages 25 to ≥95 years.[2] (A) Sequential growth ratio of CVD mortality by age groups in men and women. (B) Sequential growth ratios of cancer mortality by age groups in men and women. Abbreviations as in Figure 2.

CENTRAL ILLUSTRATION **Synergistic Effects of Biological Aging Process on Aging-Related Cardiovascular Disease Risk**



Zhao D, et al. JACC: Asia. 2024;4(5):345-358.

The impact of biological aging on aging-related CVD may be a synergistic effect of the hypothetical intrinsic biological aging process, status of modifiable risk factors, and the levels of socioeconomic development. CVD = cardiovascular disease.

different organs or systems have unique hallmarks and "clocks" in the aging process.

One of the most significant knowledge gaps in the field of biological aging research revolves around the translation of aging specific biomarkers and functional parameters into human-level assessments. This includes exploring the intricate relationships among hallmarks of biological aging and recognizing that different individuals may follow unique aging roadmaps. This would not only facilitate a deeper understanding of the aging process but also pave the way for more precise interventions and personalized strategies to promote healthy aging.

HIGHLIGHTS

- Biological aging process underlying chronological aging may play critical role in aging-related CVD.
- Aging-related CVD should be a synergistic effect of risk factors and intrinsic biological aging process.
- The synergistic effect of risk factors and intrinsic biological aging process should be modifiable.
- There are substantial knowledge gaps between the biological aging hallmarks and aging-related diseases in humans.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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

ADDRESS FOR CORRESPONDENCE: Dr Dong Zhao, Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, No 2 Anzhen Road, Chaoyang District, Beijing 100029, China. E-mail: deezhao@vip.sina.com.

REFERENCES

1. World Health Organization. *World Health Statistics 2023: Monitoring Health for the SDGs*. Geneva, Switzerland: Sustainable Development Goals.; 2023.

2. Global Burden of Disease Collaborative Network. *Global Burden of Disease Study Results*. Seattle, WA: Institute for Health Metrics and Evaluation (IHME); 2020. Accessed September 10, 2023. http://ghdx.healthdata.org/gbdresults-tool

3. United Nations, Population Division. *World Population Prospects 2019, Volume I: Comprehensive Tables (ST/ESA/SER.A/426)*. Department of Economic and Social Affairs; 2019.

4. United Nations, Population Division. *World Population Prospects 2022: Summary of Results. (UN DESA/POP/2022/TR/NO. 3.)*. Department of Economic and Social Affairs; 2022.

5. Lopez AD, Mathers CD. Measuring the global burden of disease and epidemiological transitions: 2002-2030. *Ann Trop Med Parasitol*. 2006;100(5-6):481–499.

6. Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med*. 2015;372(14):1333–1341.

7. Hambleton IR, Caixeta R, Jeyaseelan SM, Luciani S, Hennis AJM. The rising burden of noncommunicable diseases in the Americas and the impact of population aging: a secondary analysis of available data. *Lancet Reg Health Am*. 2023;21:100483.

8. Moran A, Gu D, Zhao D, et al. Future cardiovascular disease in China: Markov model and risk factor scenario projections from the coronary heart disease policy model-China. *Circ Cardiovasc Qual Outcomes*. 2010;3(3):243–252.

9. Visseren FLJ, Mach F, Smulders YM, et al, ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227–3337.

10. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74(10):e177–e232.

11. World Heart Federation. *World Health Report 2023: Confronting the World's Number One Killer*. 2023. Geneva, Switzerland. 2023. www.worldheart.org

12. Roth GA, Abate D, Abate KH, et al, GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736–1788.

13. Wang H, Naghavi M, Allen C, et al, GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459–1544.

14. Roth GA, Mensah GA, Johnson CO, et al. GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982–3021.

15. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. Biological versus chronological aging: JACC Focus Seminar. *J Am Coll Cardiol*. 2020;75(8):919–930.

16. Liberale L, Montecucco F, Tardif JC, Libby P, Camici GG. Inflamm-ageing: the role of inflammation in age-dependent cardiovascular disease. *Eur Heart J*. 2020;41(31):2974–2982.

17. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. *Nature*. 2019;571(7764):183–192.

18. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell*. 2023;186(2):243–278.

19. Abdellatif M, Rainer PP, Sedej S, Kroemer G. Hallmarks of cardiovascular ageing. *Nat Rev Cardiol*. 2023;20:754–777. https://doi.org/10.1038/s41569-023-00881-3

20. Wang H, Abbas KM, Abbasifard M, et al. GBD 2019 Demographics Collaborators. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1160–1203.

21. Amuthavalli Thiyagarajan J, Mikton C, Harwood RH, et al. The UN Decade of healthy ageing: strengthening measurement for monitoring health and wellbeing of older people. *Age Ageing*. 2022;51(7):afac147.

22. Adams JM, White M. Biological ageing: a fundamental, biological link between socio-economic status and health? *Eur J Public Health*. 2004;14(3):331–334.

23. Calimport SRG, Bentley BL, Stewart CE, et al. To help aging populations, classify organismal senescence. *Science*. 2019;366(6465):576–578.

24. Kennedy BK, Berger SL, Brunet A, et al. Geroscience: linking aging to chronic disease. *Cell*. 2014;159:709–713.

25. Anders JL, Newman AB. Telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither? *Epidemiol Rev*. 2013;35(1):112–131.

26. Belsky DW, Caspi A, Corcoran DL, et al. DunedinPACE, a DNA methylation biomarker of the pace of aging. *eLife*. 2022;11:e73420.

27. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol*. 2013;14(10):R115.

28. Fortier C, Sidibé A, Desjardins MP, et al. Aortic-brachial pulse wave velocity ratio: a blood pressure-independent index of vascular aging. *Hypertension*. 2017;69(1):96–101.

29. Ohkuma T, Ninomiya T, Tomiyama H, et al. Collaborative Group for J-BAVEL (Japan Brachial-Ankle Pulse Wave Velocity Individual Participant Data Meta-Analysis of Prospective Studies). Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: an individual participant data meta-analysis. *Hypertension*. 2017;69(6):1045–1052.

30. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. *Circ Res*. 2018;123(7):825–848.

31. Ball RL, Feiveson AH, Schlegel TT, Starc V, Dabney AR. Predicting "heart age" using electrocardiography. *J Pers Med*. 2014;4(1):65–78.

32. Shaw LJ, Raggi P, Berman DS, Callister TQ. Coronary artery calcium as a measure of biologic age. *Atherosclerosis*. 2006;188(1):112–119.

33. Cuende JI, Cuende N, Calaveras-Lagartos J. How to calculate vascular age with the SCORE project scales: a new method of cardiovascular risk evaluation. *Eur Heart J*. 2010;31(19):2351–2358.

34. Cohen AA, Kennedy BK, Anglas U, et al. Lack of consensus on an aging biology paradigm? A global survey reveals an agreement to disagree, and the need for an interdisciplinary framework. *Mech Ageing Dev*. 2020;191:111316.

35. Savji N, Rockman CB, Skolnick AH, et al. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *J Am Coll Cardiol*. 2013;61(16):1736–1743.

36. Study Group of Atherosclerosis. Atherosclerosis in coronary arteries of 7159 cases and aortas of 2044 cases: an autopsy study. *Chin J Pathol*. 1983;2:81–869 (in Chinese).

37. Kimura H, Takao M, Suzuki N, Kanemaru K, Mihara B, Murayama S. pathologic study of intracranial large artery atherosclerosis in 7260 autopsy cases. *J Stroke Cerebrovasc Dis*. 2017;26(12):2821–2827.

38. Rahimi R, Singh MKC, Noor NM, et al. Manifestation of coronary atherosclerosis in Klang Valley, Malaysia: an autopsy study. *J Atheroscler Thromb*. 2018;25(5):405–409.

39. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366(4):321–329.

40. Wang Y, Liu J, Wang W, et al. Lifetime risk of stroke in young-aged and middle-aged Chinese population: the Chinese Multi-Provincial Cohort Study. *J Hypertens*. 2016;34(12):2434–2440.

41. Feigin VL, Nguyen G, Cercy K, et al. GBD 2016 Lifetime Risk of Stroke Collaborators. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *N Engl J Med*. 2018;379(25):2429–2437.

42. Satoh M, Ohkubo T, Asayama K, et al. EPOCH-JAPAN Research Group. Lifetime risk of stroke and coronary heart disease deaths according to blood pressure level: EPOCH-JAPAN (Evidence for Cardiovascular Prevention From Observational Cohorts in Japan). *Hypertension*. 2019;73(1):52–59.

43. Kaptoge S, Pennells L, De Bacquer D, et al. WHO CVD Risk Chart Working Group. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health*. 2019;7(10):e1332–e1345.

44. Ueda P, Woodward M, Lu Y, et al. Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys. *Lancet Diabetes Endocrinol*. 2017;5(3):196–213.

45. Zhao D, Liu J, Xie W, Qi Y. Cardiovascular risk assessment: a global perspective. *Nat Rev Cardiol*. 2015;12(5):301–311.

46. Gorenoi V, Hagen A. Overview of risk-estimation tools for primary prevention of cardiovascular diseases in European populations. *Cent Eur J Public Health*. 2015;23(2):91–99.

47. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133(11):1104–1114.

48. Karlstaedt A, Moslehi J, de Boer RA. Cardio-onco-metabolism: metabolic remodeling cardiovascular disease and cancer. *Nat Rev Cardiol*. 2022;19(6):414–425.

49. Abebe F, Schneider M, Asrat B, Ambaw F. Multimorbidity of chronic non-communicable diseases in low- and middle-income countries: a scoping review. *J Comorb*. 2020;10:2235042X20961919.

50. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908:244–254.

51. Fulop T, Larbi A, Pawelec G, et al. Immunology of aging: the birth of inflammaging. *Clin Rev Allergy Immunol*. 2023;64(2):109–122.

KEY WORDS aging, biological aging, cardiovascular disease, chronological aging