**Clinical Medicine & Research**
**Volume 24, Number 2: 80-86**
©2026 Marshfield Clinic-Sanford Health
clinmedres.org

Review

# Longevity

Shereif H. Rezkalla, MD, FACP, FACC and Robert A. Kloner, MD, PhD, FACC

Longevity is defined as living a longer and healthier life. Longevity contributes to the vitality of a community, which is crucial for improving societal well-being and healthcare outcomes. In this narrative review, we report on the accepted guidelines for preventive medical management, adopting general measures of a healthy lifestyle, and discussing suggested potential therapy for improving a long healthy life. Many studies on aging revealed that longevity is multifactorial and includes telomere attrition, mitochondrial dysfunction, and loss of intercellular communication. The first steps to achieving a long and healthy life include lifestyle modification and appropriate medical care and follow up to achieve a lifelong normal blood pressure, low low-density lipoprotein, avoid smoking, manage diabetes, and follow up of all accepted medical guidelines. This should include maintaining good physical activity, appropriate nutrition, healthy sleep patterns, and managing various life stressors. There is a suggestion that intermittent fasting in humans may reduce the risk of some age-related diseases and improve longevity. In this report we will discuss these factors as well as some medications that are linked to longevity, such as metformin, rapamycin, lithium, and certain vitamins. In the absence of clear guidelines for longevity, and in the current environment of primary care shortage, we hope this report will assist primary care providers in focusing on this challenge.

**Keywords:** Aging; Longevity; Lifespan

The term longevity refers to the ability to live a long life beyond the species-specific average age at death. Longevity is a complex, multifactorial process influenced by genetics, environment, and lifestyle.[1] Longevity medicine is the medical science in healthcare that focuses on understanding and promoting longevity, emphasizing the importance of living a long and healthy life. Its goal is to prevent or delay age-related diseases. Life expectancy is considered the average number of years a person is expected to live in a specific country or region. The longest life expectancy is in the region of Hong Kong, China at 85.8 years, and lowest is in the African country of Nigeria at 54.8 years. In general, and in most localities, longevity in women is greater than in men by about 5-6 years. True longevity is a collective effort, achieved by nurturing community well-being so that all individuals can live longer, healthier lives.

Aging is a progressive biological process that leads to irreversible decline in the cellular function across the entire body. During the lifespan of a human being, there is a continuous process of cell death and cell repair to achieve a balanced normal organism. With the aging process, many biologic changes occur such as telomere attrition (the progressive shortening of telomeres), genomic instability, loss of proteostasis (the process that balances protein synthesis and degradation), mitochondrial dysfunction, and loss of intercellular communications. These processes contribute to cellular senescence, in which cells stay alive but fail to function. The number of senescent cells increase with age. Oxidative stress, free oxygen radicals, and low-grade inflammation promote the number of senescent cells. This in turn will inhibit tissue repair and accelerate aging.[2]

**Corresponding Author:** Shereif Rezkalla, MD, Sanford Health Marshfield Clinic Research Institute 1000 North Oak Avenue, Marshfield, Wisconsin, USA, E-mail: rezkalla.shereif@marshfieldresearch.org

**Financial support:** Dr. Kloner's work was supported in part by the Francis Bacon Foundation and the Pasadena Community Foundation-John and Lucille Crumb Medical Research Endowment to Huntington Medical Research Institutes (HMRI), and by the Marylou Ingram Endowment to HMRI.

**Disclosure:** The authors have no conflicts of interest related to this work to report.

Received: February 3, 2026
Revised: April 23, 2026
Accepted: May 14, 2026

doi:10.3121/cmr.2026.2111

## Telomere Shortening

While aging is a multifactorial process, telomere shortening is a well-studied condition and can be measured with laboratory methods. Telomeres are located at the end of the chromosome and provide protection to it. With each cell division, telomeres shorten, acting as a cellular clock; when they become critically short, the cell can no longer divide, and it deteriorates or dies. Oxidative stress and systemic inflammation accelerate telomere shortening, while physical activity and stress management can slow the process of telomere attrition, resulting in a longer life span.[3] There is also evidence that vitamin D may preserve telomere length.

In an in-depth review of studies, many factors will affect telomere length and longevity. Exercise, calorie restriction, stopping smoking, following a Mediterranean diet, and meditation are among the many physical factors that may prolong telomeres and improve aging.[4] This is in addition to genetic factors, which explain the longer life spans in many parts of the world. For example, a male, age 60 years, from Nicoya in Costa Rica has a 5% chance of becoming a centenarian.[5] Of note, is that the telomere shortening rate, not the initial telomere length is more predictable of longevity.[6]

Zhou et al.[7] studied 333,865 adults with a mean age of 56, following them for about 14 years. Longevity, as well as telomere length were recorded. Telomere length was associated with longer life, and physical activity improved both long life and telomere length. Telomere length can be accurately measured utilizing leucocyte telomere length.[8] The test is commercially available in many laboratories with an order from a health care provider.

In this report, we will discuss the factors that promote a long healthy life, identifying long lifespan and improving health span. The source for the literature review was PubMed. Key words included longevity, aging, preventive medicine, and lifestyle. The search period was from 2000 to 2025. Initially, only titles were reviewed; then clinically relevant abstracts were read. Key articles were critically read and included as the basis for this report.

## Generally Accepted Medical Care

In the last century, major advances in medical care are now a reality in most health care systems. This has led to a significant prolongation of the life span in the US.[9] Life and health expectancy are now achievable in the elderly without significant increase in health care spending.[10] Lifestyle modifications to promote longevity include preventive cardiology and cancer screening to detect early malignancy. Optimal blood pressure control is one of the major goals throughout a person's life.[11] Smoking adversely affects life span, and quitting smoking leads to an increased life span. The younger someone is when they quit, the more years they gain in life expectancy. Even those individuals who quit at age 65 years or older can claim some benefits.[12] Smoking cessation counseling should be a pivotal discussion during primary care visits.

A very low LDL controls vascular atherosclerotic disease, with a low incidence of myocardial infarction, stroke, and peripheral vascular disease,[13] resulting in a longer and healthier life span. PCSK9 inhibitors, in addition to lowering LDL, will also lower lipoprotein alpha, a highly atherogenic particle with a clear longevity benefit. Weight management and diabetes control are also important in longevity management.

## Physical Activity

Maintaining good physical activity throughout one's life is a key factor in improving longevity. Fan et al.[14] examined 2,626 adults, age 65 years or older, from the China Longitudinal Health Longevity Survey. Data were collected from 2011—2018. All patients had at least two chronic diseases by self-report. Those patients who were engaged in regular physical activity had a 41% reduction in all-cause mortality. Ruy Yu et al.[15] conducted a meta-analysis of 85 studies from various parts of the world. The studies investigated the association between physical activity during adult life and total mortality risk later in life. Active individuals had 20%-40% lower risk of all cause mortality. A reduction in cardiovascular mortality appears to contribute to the longevity benefit. The benefit of physical activity also extends to the very old. Yim et al.[16] followed more than 22,000 individuals, aged 80 years or older, for about two decades. Those individuals who maintained good physical activity or switched from inactive to active at this advanced age had longer survival times.

In a study of 272,550 participants in the US, achieving 15 Metabolic Equivalent of Task (MET) hours of activity per week was associated with a significant increase in survival. While racquet sports and running were associated with better results compared with less intense activities, such as golf or swimming, all types of activity were associated with lowered mortality risk.[17] It may be better that individuals choose a sport they will be able to sustain to gain benefit for the rest of their lives.

## Healthy Sleep Patterns

A healthy sleep pattern is an important aspect of a healthy lifestyle and is associated with good cognitive function. Li et al.[18] studied sleep patterns in 10,768 subjects participating in the China Health and Retirement Longitudinal Study. Cognitive function of individuals was evaluated at baseline and at follow-up and was correlated with sleep pattern. Duration of sleep had an inverted U-shaped relationship with cognitive function. The best sleep duration was about 6 hours. Cognitive function decreased with shorter or longer sleep time. Sleep quality had a positive linear relationship with cognitive score.[18] Thus, the best practice is to have 6 hours of quality sleep to achieve the best cognitive score.

In another study from the Chinese Longitudinal Healthy Longevity Survey, 3094 subjects were followed for a median follow up of 6 years. Leisure activity and sleep time were correlated with cognitive function.[19] A noticeably short or exceptionally long sleep time was associated with increased risk of cognitive impairment. High level leisure activities, such as swimming, running, gardening, and reading were associated with a reduced risk of cognitive impairment. Of note is that leisure activity was only light physical activity, such as social and cultural activities, some housework, gardening, watching television, or raising domestic pets. So, it is important for individuals to engage in light physical activity during the day and attempt to maintain a healthy sleep pattern at night.

## Stress and Longevity

Careful and comprehensive review of the literature shows a close relationship between various kinds of emotional stress, such as post-traumatic stress disorder, and early dementia.[20] Stress management should include all phases of the life span, starting from early phases.[21] In the study of the Rugao Longitudinal Aging Cohort, 852 elderly individuals were studied for the stress effect on the motor risk syndrome. This is a syndrome of perceived stress and slow gate; the study showed strong correlation between stress and development of motor cognitive risk syndrome.[22] Social stressors across the life span were associated with shorter telomeres, suggesting a plausible mechanism for the relationship between stress and dementia.[23] While it is difficult to completely eliminate stress, engaging in organized yoga-type activities may help manage stress. Yoga's effect on preserving telomere length, reducing oxidative stresses, and enhancing immune function may improve quality of life and extend health span.[24]

## Intermittent Fasting

Intermittent fasting is a pattern that involves alternating between eating and fasting. Many protocols exist, such as fasting for 24 hours once or twice a week, 36 hours of fasting followed by 8 hours of eating, or alternate day fasting. Whatever the pattern is, there are many benefits for humans. Intermittent fasting can lead to reduced inflammation, decreased oxidative stress, reduced risk of diabetes with reduction in insulin resistance, which can lead to better control of blood pressure. There are also many benefits related to malignancy, such as decreased cancer risk and decreased side effects of chemotherapy, as well as making malignant cells more susceptible to chemotherapy.[25]

## Medications and Longevity

A fundamental factor that prolongs a healthy life is controlling cardiovascular risk factors.[26] Statins and medications such as PCSK-9 inhibitors to lower low density lipoproteins (LDL) are the backbone of a healthy life with decreased acute cardiac events and lower mortality.[13] More efforts need to be utilized by both physicians and patients to achieve low LDL and assure good patient compliance. It is also prudent to start in early phases of life.[27] Medications to normalize blood pressure are equally important. For women over age 65 years, keeping systolic blood pressure below 130 mm Hg was found to increase longevity.[28] Controlling diabetes is essential in avoiding its complications, hopefully resulting in a long healthy life.[29]

In addition to these main pillars of medical care that are accepted for prolonging the life span and the health span of the population, there are some medications with the potential of improving longevity, which we discuss in the following section.

*Metformin*

Biguanide is a class of synthesized drugs that originated from compounds found in the French lilac in the 17th century. While *Galega officinalis* is an herb used in herbal medicine, biguanides are chemical derivatives of it that were later synthesized and developed into pharmaceutical agents. Dimethylbiguanide (metformin) was synthesized in 1922, and in the 1950s it was utilized in the management of diabetes mellitus.[30] It decreases hepatic glucose production, intestinal glucose uptake, and hepatic gluconeogenesis. It is the mainstay of therapy in treating type 2 diabetes.[31]

With its widespread use, metformin has other associated benefits. Among older adults with diabetes, it demonstrated a benefit in cognitive function. Tze Pin et al.[32] studied 365 patients, age 55 years and above, with diabetes and followed them for up to 6 years. Diabetic patients who used metformin showed better cognition compared to non-users. Min Guo et al.[33] divided a cohort of 58 patients with diabetes and depression into a treatment group with metformin or placebo and followed them for 24 weeks. At the end of the study, cognitive performance was measured by the Wechsler Memory Scale-Revised. Despite the small number of patients and the relatively short study period, the metformin group had an improvement in cognitive function.

In addition to improving cognitive function, metformin has other effects that support longevity. Libby et al.[34] studied about 8,000 patients with type 2 diabetes who were followed for about 10 years. Cancer was diagnosed in 7.3% of metformin users, compared with 11.6% in non-users ($P$ <0.001). After adjusting for many variables, including smoking, metformin use was associated with a clear reduced risk of cancer development. In a larger cohort of 800,000 individuals from the Taiwan national health insurance data, people with diabetes who used metformin had a reduced incidence of colorectal, liver, and pancreatic cancer.[356] These beneficial effects in improving cognitive function and decreasing the incidence of cancer, among other benefits in longevity, strengthen a link between metformin use and longevity.

Stevenson-Hoare et al.[36] studied medical records of patients in Wales (UK) who had diabetes. They compared patients treated with metformin to others treated with sulphonylurea. Metformin appeared to have benefit in short-term and long-term follow up.

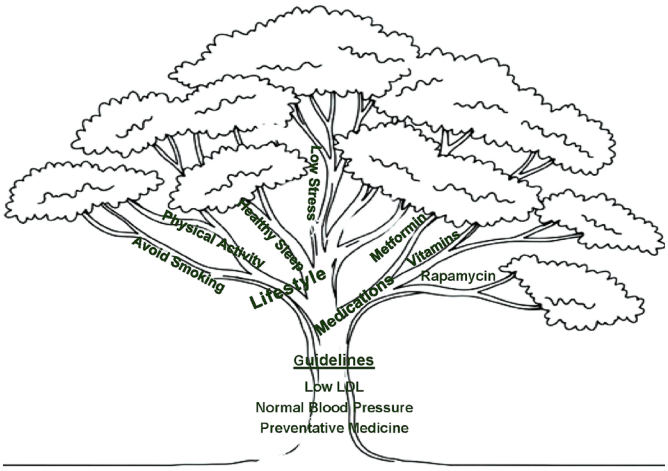


**Figure 1.** Depiction of various measures to be considered in the best approach for longevity.

Short-term patients had better hemoglobin A1c, and with 5-year follow up, they had longer survival and lower incidence of cancer. With the clear link between metformin and longevity, the TAME study was designed, in which 3000 non-diabetic individuals, age 65-80 years, will be randomized to metformin or placebo and will be followed for 6 years. The end point will be a composite of myocardial infarction, congestive heart failure, stroke, cancer, cognitive function, and mortality.[37] The study is approved by the Food and Drug Administration (FDA), but it was not yet launched. It will have a definitive answer to the true benefit of metformin, including those patients without diabetes.

*Rapamycin*

Rapamycin (sirolimus) is an FDA-approved drug with immune modulating properties and is used as an immunosuppressant in organ transplant patients.[38] The drug has shown consistently positive effects on longevity in mice.[39-41] Only one study was conducted in humans. In that study, 333 adults received off-label rapamycin with the only conclusion being that the drug is safe when used in healthy adults. The dose used was variable, and the frequency of administration was inconsistent. The endpoint was only safety. No other data were collected such as benefit in cognition or longevity. Data endpoints were subjective, and it is difficult to draw any conclusions about its longevity benefit in humans.[42] Unless there is a well-organized, double-blind, randomized trial in humans, we cannot suggest any human benefit.

*Lithium*

There is a link between lithium and a longer life span in both animals and humans.[43] This was reported in a small amount of lithium that may be present in tap water in some communities. It also showed that lithium may increase telomere length in humans.[44] Lithium also resulted in beneficial metabolic effects in drosophila.[45] In a review and meta-analysis of 76 peer reviewed studies, while depression was associated with cognitive control defect, there was no effect of depression medications on longevity, including lithium therapy.[46] The dose, however, used in depression therapy was much higher than the very low dose that showed some benefit, mainly in animal studies. While we believe it is a link, there is a clear need for further human studies to prove its potential benefit in longevity.

*Vitamins and Nutrition*

People need to avoid malnutrition and include in their diet all essential nutrients.[47] In a review among centenarians, their diet was shown to normally be diverse, with controlled salt and containing all essential dietary recommendations, including milk and grains.[48] Special food elements (referred to as superfoods), like blueberries, spinach, avocado, pomegranates, and dark chocolate are associated with longer telomere length.[49] While all vitamins are important, folate, vitamin B12, and vitamin D3 are associated with longer telomere length and are clearly linked to longevity.[50-53]

In an epidemiologic study, Mao et al.[51] investigated the level of circulating vitamin D in elderly Chinese adults, median age 93 years. The levels were significantly higher than levels in the normal population.

The VITAL study was designed to determine whether vitamin D3 supplementation can affect the rate of cancer and the incidence of cardiovascular disease. They randomized 25,871 individuals to receive vitamin D3, omega-3 fatty acids, or placebo in a 2 x 2 factorial design, with median follow-up duration of 5.3 years. While there was no benefit in the primary endpoints, there was a reduction in total all-cause mortality. Thus, patients who received vitamin D3 appeared to have a benefit in longevity.[54]

Of note is the study by Dai et al.[48] about the health in centenarians and near-centenarians (ages 95-118 years); 43% had a history of hypertension and 22% had diabetes. Thus, chronic diseases, if managed properly, may still provide individuals with a good chance of being a centenarian.

Following myocardial infarction, the area supplied by the occluded coronary artery will die and is replaced by non-functional fibrous tissue by stimulating endogenous time repair or by infusing intracoronary human stem cell-derived cardiac myocytes, or live functional cardiac tissue may be produced. Cell transplant therapy had extensive laboratory studies and a few human trials. Despite slow progress, cell transplant therapy provides hope for organ repair, which may provide a future for a longer, healthy life.[55] Various measures to be considered in the best approach for longevity are depicted in Figure 1.

This review examines the pathophysiology and clinical management of a long healthy lifespan (longevity). While

established interventions, such as early cancer detection and atherosclerotic vascular disease prevention, are addressed, many proposed longevity measures lack validation by controlled randomized trials. As the field of longevity medicine becomes more well-established, rigorous studies will generate clearer evidence, facilitating the development of definitive, evidence-based recommendations.

## Conclusion

Longevity is an emerging goal and challenge in today's medical care that should begin with generally accepted medical guidelines. Maintaining LDL at the recommended medical guidelines should be implemented early in life. Optimal blood pressure should be a goal throughout one's lifetime. Avoid smoking and controlling diabetes are other important aspects of better longevity. All other preventive measures, such as mammography for early prediction of breast cancer and colonoscopy for early management of colon cancer, should be followed. Maintaining a satisfactory level of physical activity throughout a lifetime is a main pillar for a long, healthy life. Multiple controlled studies have proven organized physical activity leads to a significant decrease in all-cause mortality. A healthy sleep pattern and a low stress level are other pillars for longevity.

Many medications were linked to a long healthy life, such as metformin, rapamycin, lithium, and some vitamins. The main medication with immense potential is metformin. A TAME study[37] was designed as a controlled prospective study to investigate the potential benefit of the drug and will have a definitive answer for its effect on longevity. Many factors will provide a long healthy life, with the potential for a new specialty in medical care called "Longevity Medicine." The use of information system support and the assistance of artificial intelligence may help in integrating guidance into clinical practice.

## Acknowledgements

The authors thank Marie Fleisner for editorial assistance with the paper and for creating the figure.

## References

1. De Benedictis G, Franceschi C. The unusual genetics of human longevity. Sci Aging Knowledge Environ. 2006;2006(10):pe20. doi:10.1126/sageke.2006.10.pe20
2. Guo J, Huang X, Dou L, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduct Target Ther. 2022;7(1):391. doi:10.1038/s41392-022-01251-0
3. Boccardi V. From telomeres and senescence to integrated longevity medicine: redefining the path to extended healthspan. Biogerontology. 2025;26(3):107. doi:10.1007/s10522-025-10246-7
4. Vidacek NŠ, Nanic L, Ravlic S, et al. Telomeres, Nutrition, and Longevity: Can We Really Navigate Our Aging?. J Gerontol A Biol Sci Med Sci. 2017;73(1):39-47. doi:10.1093/gerona/glx082
5. Ruiz-Narváez EA, Baylin A, Azofeifa J, Leal A, Rosero-Bixby L. Diet and Leukocyte Telomere Length in a Population with Extended Longevity: The Costa Rican Longevity and Healthy Aging Study (CRELES). Nutrients. 2021;13(8):2585. doi:10.3390/nu13082585
6. Whittemore K, Vera E, Martínez-Nevado E, Sanpera C, Blasco MA. Telomere shortening rate predicts species life span. Proc Natl Acad Sci U S A. 2019;116(30):15122-15127. doi:10.1073/pnas.1902452116
7. Zhou HH, Jin B, Liao Y, et al. Associations of Various Physical Activities with Mortality and Life Expectancy are Mediated by Telomere Length. J Am Med Dir Assoc. 2024;25(3):431-438.e15. doi:10.1016/j.jamda.2023.08.002
8. Thai NQN, LaCroix AZ, Haring B, et al. The association of leukocyte telomere length with exceptional longevity among older women. Geroscience. 2024;46(2):2083-2092. doi:10.1007/s11357-023-00964-6
9. Health United States, 2001: with urban and rural health chart book. Hyattsville, MD: National Center for Health Statistics, 200. DHHS-publication: 01-1232.
10. Lubitz J, Cai L, Kramarow E, Lentzner H. Health, life expectancy, and health care spending among the elderly. N Engl J Med. 2003;349(11):1048-1055. doi:10.1056/NEJMsa020614
11. Lu Y, Ma Y. Optimal Blood Pressure Control for Optimal Longevity: Balancing Cardiovascular and Cognitive Outcomes. Circ Cardiovasc Qual Outcomes. 2024;17(6):e011135. doi:10.1161/CIRCOUTCOMES.124.011135
12. Le TTT, Mendez D, Warner KE. The Benefits of Quitting Smoking at Different Ages. Am J Prev Med. 2024;67(5):684-688. doi:10.1016/j.amepre.2024.06.020
13. Rezkalla SH, Kloner RA. Low HDL-The Challenge. Clin Med Res. 2025;23(2):60-66. doi:10.3121/cmr.2025.1970
14. Fan B, Ren K, Li L. The joint effect of weight-adjusted waist index and physical activity on all-cause mortality in Chinese elderly patients with multimorbidity: A study based on the CLHLS from 2011 to 2018. PLoS One. 2025;20(6):e0325886. doi:10.1371/journal.pone.0325886
15. Yu R, Duncombe SL, Nemoto Y, Araujo RH, Chung HF, Mielke GI. Physical activity trajectories and accumulation over adulthood and their associations with all-cause and cause-specific mortality: a systematic review and meta-analysis. Br J Sports Med. 2025;59(17):1228-1241. doi:10.1136/bjsports-2024-109122

16. Yin R, Wang Y, Li Y, et al. Changes in physical activity and all-cause mortality in the oldest old population: Findings from the Chinese Longitudinal Healthy Longevity Survey (CLHLS). Prev Med. 2023;175:107721. doi:10.1016/j.ypmed.2023.107721
17. Watts EL, Matthews CE, Freeman JR, et al. Association of Leisure Time Physical Activity Types and Risks of All-Cause, Cardiovascular, and Cancer Mortality Among Older Adults. JAMA Netw Open. 2022;5(8):e2228510. doi:10.1001/jamanetworkopen.2022.28510
18. Li M, Wang N, Dupre ME. Association between the self-reported duration and quality of sleep and cognitive function among middle-aged and older adults in China. J Affect Disord. 2022;304:20-27. doi:10.1016/j.jad.2022.02.039
19. Li Q, Huo JM, Jia CX, Jia FF. Relationship between development trajectories of leisure activity and sleep time on incident cognitive impairment: A study based on the Chinese Longitudinal Healthy Longevity Survey (CLHLS). J Alzheimers Dis. 2025;104(2):573-584. doi:10.1177/13872877251318023
20. Luo J, Beam CR, Gatz M. Is Stress an Overlooked Risk Factor for Dementia? A Systematic Review from a Lifespan Developmental Perspective. Prev Sci. 2023;24(5):936-949. doi:10.1007/s11121-022-01385-1
21. Entringer S, Heim C. A Brief Historic Review of Research on Early Life Stress and Inflammation across the Lifespan. Neuroimmunomodulation. 2025;32(1):24-35. doi:10.1159/000542676
22. Cao YF, Shi GP, Zhang H, et al. Association between Perceived Stress and Motoric Cognitive Risk Syndrome in an Elderly Population: Rugao Longevity and Aging Study. Dement Geriatr Cogn Disord. 2024;53(2):74-82. doi:10.1159/000537937
23. Willis M, Reid SN, Calvo E, Staudinger UM, Factor-Litvak P. A scoping systematic review of social stressors and various measures of telomere length across the life course. Ageing Res Rev. 2018;47:89-104. doi:10.1016/j.arr.2018.07.006
24. Chen Q. Neurobiological and anti-aging benefits of yoga: A comprehensive review of recent advances in non-pharmacological therapy. Exp Gerontol. 2024;196:112550. doi:10.1016/j.exger.2024.112550
25. Strilbytska O, Klishch S, Storey KB, Koliada A, Lushchak O. Intermittent fasting and longevity: From animal models to implication for humans. Ageing Res Rev. 2024;96:102274. doi:10.1016/j.arr.2024.102274
26. van Oort S, Beulens JWJ, van Ballegooijen AJ, Burgess S, Larsson SC. Cardiovascular risk factors and lifestyle behaviours in relation to longevity: a Mendelian randomization study. J Intern Med. 2021;289(2):232-243. doi:10.1111/joim.13196
27. Jaspers NEM, Visseren FLJ, Numans ME, et al. Variation in minimum desired cardiovascular disease-free longevity benefit from statin and antihypertensive medications: a cross-sectional study of patient and primary care physician perspectives. BMJ Open. 2018;8(5):e021309. doi:10.1136/bmjopen-2017-021309
28. Haring B, Andrews CA, Hovey K, et al. Systolic Blood Pressure and Survival to Very Old Age: Results From the Women's Health Initiative. Circulation. 2024;149(20):1568-1577. doi:10.1161/CIRCULATIONAHA.123.067302
29. Chan JCN, Yang A, Chu N, Chow E. Current type 2 diabetes guidelines: Individualized treatment and how to make the most of metformin. Diabetes Obes Metab. 2024;26 Suppl 3:55-74. doi:10.1111/dom.15700
30. Thomas I, Gregg B. Metformin; a review of its history and future: from lilac to longevity. Pediatr Diabetes. 2017;18(1):10-16. doi:10.1111/pedi.12473
31. Bailey CJ. Metformin: historical overview. Diabetologia. 2017;60(9):1566-1576. doi:10.1007/s00125-017-4318-z
32. Ng TP, Feng L, Yap KB, Lee TS, Tan CH, Winblad B. Long-term metformin usage and cognitive function among older adults with diabetes. J Alzheimers Dis. 2014;41(1):61-68. doi:10.3233/JAD-131901
33. Guo M, Mi J, Jiang QM, et al. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clin Exp Pharmacol Physiol. 2014;41(9):650-656. doi:10.1111/1440-1681.12265
34. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care. 2009;32(9):1620-1625. doi:10.2337/dc08-2175
35. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC Cancer. 2011;11:20. doi:10.1186/1471-2407-11-20
36. Stevenson-Hoare J, Leonenko G, Escott-Price V. Comparison of long-term effects of metformin on longevity between people with type 2 diabetes and matched non-diabetic controls. BMC Public Health. 2023;23(1):804. Pdoi:10.1186/s12889-023-15764-y
37. Konopka AR, Miller BF. Taming expectations of metformin as a treatment to extend healthspan. Geroscience. 2019;41(2):101-108. doi:10.1007/s11357-019-00057-3
38. Sharp ZD, Strong R. Rapamycin, the only drug that has been consistently demonstrated to increase mammalian longevity. An update. Exp Gerontol. 2023;176:112166. doi:10.1016/j.exger.2023.112166

39. Blagosklonny MV. DNA- and telomere-damage does not limit lifespan: evidence from rapamycin. Aging (Albany NY). 2021;13(3):3167-3175. doi:10.18632/aging.202674
40. Baghdadi M, Nespital T, Monzó C, Deelen J, Grönke S, Partridge L. Intermittent rapamycin feeding recapitulates some effects of continuous treatment while maintaining lifespan extension. Mol Metab. 2024;81:101902. doi:10.1016/j.molmet.2024.101902
41. Wolff CA, Lawrence MM, Porter H, et al. Sex differences in changes of protein synthesis with rapamycin treatment are minimized when metformin is added to rapamycin. Geroscience. 2021;43(2):809-828. doi:10.1007/s11357-020-00243-8
42. Kaeberlein TL, Green AS, Haddad G, et al. Evaluation of off-label rapamycin use to promote healthspan in 333 adults. Geroscience. 2023;45(5):2757-2768. doi:10.1007/s11357-023-00818-1
43. Zarse K, Terao T, Tian J, Iwata N, Ishii N, Ristow M. Low-dose lithium uptake promotes longevity in humans and metazoans. Eur J Nutr. 2011;50(5):387-389. doi:10.1007/s00394-011-0171-x
44. Coutts F, Palmos AB, Duarte RRR, et al. The polygenic nature of telomere length and the anti-ageing properties of lithium. Neuropsychopharmacology. 2019;44(4):757-765. doi:10.1038/s41386-018-0289-0
45. Castillo-Quan JI, Li L, Kinghorn KJ, et al. Lithium Promotes Longevity through GSK3/NRF2-Dependent Hormesis. Cell Rep. 2016;15(3):638-650. doi:10.1016/j.celrep.2016.03.041
46. Dotson VM, McClintock SM, Verhaeghen P, et al. Depression and Cognitive Control across the Lifespan: a Systematic Review and Meta-Analysis. Neuropsychol Rev. 2020;30(4):461-476. doi:10.1007/s11065-020-09436-6
47. Starck CS, Cassettari T, Beckett E, Duve E, Fayet-Moore F. Identification of Priority Nutrients in the US: Targeting Malnutrition to Address Diet-Related Disease Across the Lifespan. Nutrients. 2025;17(12):1957. doi:10.3390/nu17121957
48. Dai Z, Lee SY, Sharma S, et al. A systematic review of diet and medication use among centenarians and near-centenarians worldwide. Geroscience. 2024;46(6):6625-6639. doi:10.1007/s11357-024-01247-4
49. Boccardi V, Polom J. Searching for Beauty and Health: Aging in Women, Nutrition, and the Secret in Telomeres. Nutrients. 2024;16(18):3111. doi:10.3390/nu16183111
50. Praveen G, Shalini T, Sivaprasad M, Reddy GB. Relative telomere length and mitochondrial DNA copy number variation with age: Association with plasma folate and vitamin B12. Mitochondrion. 2020;51:79-87. doi:10.1016/j.mito.2020.01.007
51. Mao C, Li FR, Yin ZX, et al. Plasma 25-Hydroxyvitamin D Concentrations Are Inversely Associated with All-Cause Mortality among a Prospective Cohort of Chinese Adults Aged ≥80 Years. J Nutr. 2019;149(6):1056-1064. doi:10.1093/jn/nxz041
52. Bischoff-Ferrari HA, de Godoi Rezende Costa Molino C, Rival S, et al. DO-HEALTH: Vitamin D3 - Omega-3 - Home exercise - Healthy aging and longevity trial - Design of a multinational clinical trial on healthy aging among European seniors. Contemp Clin Trials. 2021;100:106124. doi:10.1016/j.cct.2020.106124
53. Saenz AD; Mass General Brigham AI Governance Committee, Centi A, et al. Establishing responsible use of AI guidelines: a comprehensive case study for healthcare institutions. NPJ Digit Med. 2024;7(1):348. doi:10.1038/s41746-024-01300-8
54. Manson JE, Bassuk SS, Buring JE; VITAL Research Group. Principal results of the VITamin D and OmegA-3 TriaL (VITAL) and updated meta-analyses of relevant vitamin D trials. J Steroid Biochem Mol Biol. 2020;198:105522. doi:10.1016/j.jsbmb.2019.105522
55. Gerbin KA, Murry CE. The winding road to regenerating the human heart. Cardiovasc Pathol. 2015;24(3):133-140. doi:10.1016/j.carpath.2015.02.004

## Author Affiliations

*Shereif H. Rezkalla, MD, FACP, FACC[*] and Robert A. Kloner, MD, PhD, FACC[†]*

*[*]Emeritus Physician, Marshfield Clinic Research Institute, 1000 North Oak Avenue, Marshfield, Wisconsin, USA. E-mail: rezkalla.shereif@marshfieldclinic.org*
*[†]Chief Science Officer, Scientific Director of Cardiovascular Research Institute, Huntington Medical Research Institutes, Pasadena, California, USA; Professor of Medicine (Clinical Scholar), Cardiovascular Division, Dept. of Medicine, Keck School of Medicine of University of Southern California, Los Angeles, California, USA*