Clinical Interventions in Aging

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REVIEW

Addressing the Missing Links in Cardiovascular Aging

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Abstract: The aim of this manuscript is to provide a review of available options to enhance cardiovascular health and prevent cardiovascular disease (CVD) in the aging population using a systems-biology approach. These include the role of the gut microbiome, the early identification and removal of environmental toxins, and finally age related sex hormones and supplement replacement which all influence aging. Implementing such a comprehensive approach has the potential to facilitate earlier risk assessment, disease prevention, and even improve mortality. Further study in these areas will continue to advance our understanding and refine therapeutic interventions for a healthier cardiovascular aging process.

Keywords: vascular aging, cardiovascular aging, inflammaging, systems biology medicine, microbiome, toxic metals, bioidentical hormone replacement

Introduction

According to the US Bureau of the Census, individuals aged 85 and older are now the fastest growing population. It is estimated that by 2030, 20% of the population will be over 65 years of age. The life expectancy over the recent years has been declining while this demographic shift has been accompanied by a significant increase in age-related chronic diseases, particularly cardiovascular disease (CVD). It is widely accepted that atherosclerosis, a primary driver of CVD, is primarily caused by inflammation at the endovascular level, yet most treatments fail to address their cause.[1]

Aging itself is a major independent risk factor for CVD, which remains one of the leading causes of disability and death in the United States.[2] As shown in different studies, age-related arterial dysfunction was found in the absence of conventional cardiovascular risk factors, suggesting that age-related arterial dysfunction is a primary effect of advancing age.[3,4] This phenomenon persists despite best efforts to promote healthy lifestyle and pharmacological treatments. Additionally, it is worth noting that as much as 20% of individuals who develop coronary heart disease lack conventional risk factors.[5] This suggests there are still unaddressed factors missing from the current approach to patient management. Furthermore, another study showed that up to 70% of individuals who experienced myocardial infarctions were classified as low risk based on conventional 10-year coronary heart disease risk screening.[6] These findings are particularly concerning given the impact on morbidity and mortality in the United States, where the country ranks last out of 11 developed nations in terms of health care cost and avoidable mortality.[7]

Recent evidence suggests that three finite physiological responses to numerous insults exist in the human body, attributing to the pathophysiology of CVD: oxidative stress, inflammation, and ultimately vascular dysfunction.[8,9] This process, often referred to as vascular aging or "Inflammaging", encompasses the complex interplay of molecular and cellular events like immune dysregulation associated with aging and the acceleration of age-related diseases.[10] Consequently, it is essential to consider certain overlooked and novel factors that contribute to aging as a process also contributing to the origin of traditional risk factors. For example, the gut microbiome-a complex ecosystem of organisms located throughout our body organs, including the gastrointestinal tract, serving as a transducer of environmental signals to the rest of the body-contributing either to promoting or reducing systemic inflammation and age-related cardiovascular

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disease risk.[11,12] Understanding such factors is needed to be able to address them. In this manuscript the evidence behind this system-biology approach will be reviewed to help identify targets improve cardiovascular health.

The Microbiome and Cardiovascular Aging

Recent advancements in our understanding of aging have highlighted the crucial role of the gut microbiome, a complex ecosystem comprising bacteria and various other organisms, both commensal and pathogenic. Imbalances in this microbial composition have shown to influence overall health, including CVD.[13] As individuals age, there is a notable shift in the human microbiota. Two predominant bacterial phyla, Firmicutes and Bacteroidetes, play a crucial role in maintaining a healthy microbiome.[14,15] Disruptions in the balance of these organisms can significantly impact intestinal homeostasis and its communication with the rest of the body. Specifically, aging and age- related pathology including CAD appears to be linked to the relative abundance of the phyla Firmicutes, which increases with age, and a decrease in Bactericides.[16] A recent meta-analysis highlighted differences in the gut microbiota composition in coronary artery disease patients compared to healthy controls with strikingly low ratios of the Phyla Bacteroides.[17] Furthermore, the abundance of a genus of bacteria called Bifidobacterium in the microbiome that is most abundant in childhood declines with age. It has shown to up-regulate anti-inflammatory pathways and even sequester heavy metals balancing the microbiome.[18] Being able to identify such imbalances would allow targeted treatment strategies such as dietary modification, shown to promote relative abundance of Bifidobacterium, like a higher proportion of organic plant-based foods.[19] Microbiome organism makeup is now identifiable through qPCR or RNA sequencing of stool samples becoming more and more accessible.

Diets high in saturated fat and sucrose, contribute to detrimental changes in the microbiome. These dietary patterns increase intestinal permeability, allowing endotoxins like lipopolysaccharides (LPS) from gram-negative bacteria to enter the circulation.[20] Consequently, the body experiences elevated levels of reactive oxygen species (ROS) and triggers an inflammatory cascade of the three finite responses.[21] This endotoxin has been associated with various age-related inflammatory conditions, including visceral fat deposition and CVD.[22] Given that the intestinal wall houses the Peyer's patches, home to approximately 70% of the immune system, LPS prompts significant dendritic cells to initiate potent T cell–dependent responses and immune dysregulation leading to numerous inflammatory disorders.[23] A recent review demonstrated how pre and probiotics can mitigate the detrimental effects of LPS on the intestinal lining and the vasculature hence lowering such inflammation and subsequent CVD risk.[24] This intricate connection between the microbiome and systemic aging underscores the importance of considering the microbiome in not just cardiovascular medicine but all disciplines for prevention.

Another factor influencing the cardiovascular system is the accumulation of Trimethylamine-N-oxide (TMAO), an inflammatory metabolite produced by the liver in response to specific gut bacteria. Consumption of foods high in L-carnitine and choline, such as full-fat dairy, egg yolk, and red meat, can lead to the production of trimethylamine in the gut through microbial metabolism.[25] This compound is subsequently absorbed into the bloodstream, where it is metabolized by the liver into TMAO. TMAO disrupts mitochondrial function and promotes the activation of NFKb, and there is already evidence of a causal link to CVD based on animal models.[26] TMAO activates monocytes, which play a significant role in various pathways leading to atherosclerosis. Consequently, TMAO is recognized as a potential independent risk factor for CVD.[26,27] Further high plasma TMAO levels have been independently linked as risk factors for heart disease and correlated with poor prognosis in myocardial infarction according to systematic review.[28,29] Measuring this metabolite is now easily available from all of the major labs. Supplementing specific strains of probiotics have shown to lower TMAO and thereby CVD risk based on the evidence of its influence on lipid profiles, glycemia, and homocysteine further supporting this approach see Table 1.

The gut microbiome may too influence aging via its impact on toxin accumulation. The resident microbiota may interfere with bioavailability and thereby cardiotoxicity of metals via oxidative stress over the duration of lifespan. For example, animal and even human trials have provided evidence for beneficial effects exerted by certain bacteria where probiotic strains reduced the bioaccumulation of arsenic and mercury.[30] The evidence further supports the vice versa relationship where toxic exposures have shown to reduce the abundance of healthy bacterial strains of Bifidobacterium, Bacteroides, and Lactobacillus. As lifestyle and nutrition interventions are the primary steps necessary before considering medications, focusing on the microbiome offers a novel starting point. Microbiome stool testing and simple interventions like dietary changes may therefore help slow cardiovascular aging.

Table 1 Manipulating the Microbiome on CVD Risk

Species	Study Type	Subjects	Findings	Citation
Human	RCT	36	Supplementation with Lactobacillus plantarum produced a significant decrease in systolic BP, leptin, and fibrinogen in heavy smokers	Naruszewicz M, Johansson ML, Zapolska-Downar D, Bukowska H. Effect of Lactobacillus plantarum 299v on cardiovascular disease risk factors in smokers. Am J Clin Nutr. 2002 Dec;76(6):1249–55. doi: 10.1093/ajcn/76.6.1249. PMID: 12450890[31]
Human	Controlled clinical trial	24	Fermented milk with L. plantarum showed more favorable results in relation to cardiovascular risk factors such as glucose and homocysteine in postmenopausal women with MetS.	Barreto FM, Colado Simão AN, Morimoto HK, Batisti Lozovoy MA, Dichi I, Helena da Silva Miglioranza L. Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. Nutrition. 2014 Jul-Aug;30(7–8):939–42. doi: 10.1016/j.nut.2013.12.004. Epub 2013 Dec 14. PMID: 24613434[32]
Human	Meta analysis	641	Probiotic consumption significantly decreased systolic, diastolic BP, low density lipoprotein, total cholesterol and triglycerides, compared with placebo in T2DM	Hendijani F, Akbari V. Probiotic supplementation for management of cardiovascular risk factors in adults with type II diabetes: A systematic review and meta-analysis. Clin Nutr. 2018 Apr;37(2):532–541. doi: 10.1016/j.clnu.2017.02.015. Epub 2017 Feb 24. PMID: 28318686[33]
Human	RCT	46	Fiber induced probiotics negative correlation with HgA1c	Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, Fu H, Xue X, Lu C, Ma J, Yu L, Xu C, Ren Z, Xu Y, Xu S, Shen H, Zhu X, Shi Y, Shen Q, Dong W, Liu R, Ling Y, Zeng Y, Wang X, Zhang Q, Wang J, Wang L, Wu Y, Zeng B, Wei H, Zhang M, Peng Y, Zhang C. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science. 2018 Mar 9;359(6380):1151–1156. doi: 10.1126/science.aao5774. PMID: 29,590,046.[34]
Human	Observational study	21	Lp299v strain of probiotic improved vascular endothelial function and decreased systemic inflammation in men with CAD.	Malik M, Suboc TM, Tyagi S, Salzman N, Wang J, Ying R, Tanner MJ, Kakarla M, Baker JE, Widlansky ME. Lactobacillus plantarum 299v Supplementation Improves Vascular Endothelial Function and Reduces Inflammatory Biomarkers in Men With Stable Coronary Artery Disease. Circ Res. 2018 Oct 12;123(9):1091–1102. doi: 10.1161/CIRCRESAHA.118.313565. PMID: 30,355,158; PMCID: PMC6205737.[35]
Human	Systematic review	115	Lactobacillus rhamnosus GG most reduced plasma TMAO concentration	Cantero MA, Guedes MRA, Fernandes R, Lollo PCB. Trimethylamine N-oxide reduction is related to probiotic strain specificity: A systematic review. Nutr Res. 2022 Aug;104:29–35. doi: 10.1016/j.nutres.2022.04.001. Epub 2022 Apr 10. PMID: 35,588,611.[36]

Abbreviations: RCT, Randomized Controlled Trial; MetS, Metabolic Syndrome; T2DM, Type 2 Diabetes Mellitus; HgA1c, Hemoglobin A1c; BP, Blood pressure; TMAO, Trimethylamine N-oxide.

Environmental Toxins and Cardiovascular Aging

Toxic metals play a crucial role in aging and heart disease by contributing to oxidative stress and inflammation in an insidious manner.[37] One significant source of metal exposure is particulate matter in the air, which is closely associated with CVD,

contributing significantly to global mortality rates.[38] Toxic metals have been known to cause atherosclerosis and CVD underscoring the absence of measuring safe levels in all at-risk patients and implementing necessary and standard interventions. environmental exposure levels.[39] Despite banning toxic metals such as lead, its presence is still impactful due to things like international trade and vertical transmission. Bioaccumulation of mercury occurs in key visceral organs and was shown to be associated with aging and accelerated disease development in a dose dependent manner.[40] Similarly, arsenic has been found in contaminated water and contributes to CVD health outcomes from chronic exposure.[41] Recent studies have also found that these toxic metals influence earlier menopause in women, further supporting their role in cardiovascular aging and heart disease.[42] While conventional medicine mainly focuses on the symptoms of acute metal poisoning vs chronic accumulation and role in chronic disease toxic metals are still overlooked. Such critical lab screening could elicit a major missed factor responsible for heart disease progression. To effectively address toxic metal exposure, it is crucial to enhance the body's detoxification process. Not uncommon issues including nutrient depletions can further hamper the liver's ability to detoxify metals. Studies in animals and humans have shown that deficiencies in essential metals such as zinc, calcium, or iron can lead to greater absorption and toxicity of non-essential metals.[43–45] Therefore, consuming foods high in these minerals and antioxidants is of particular importance as they act as natural antagonists to the toxicity of metals such as cadmium and lead.[46] Chelation therapy, such as Ethylenediaminetetraacetic acid (EDTA) is another treatment which binds metals particularly lead. Intravenous EDTA more recently has shown to be more effective compared with placebo at reducing clinically important cardiovascular events.[47] This can be of great benefit to patients especially with progressive or refractory CVD which may be from underlying toxicity. Supportive studies show that 2 g/week slow IV infusion (over 2 hours) did not produce adverse events in humans while effectively removing such metals.

Sauna use has shown that the body's natural detoxification process through sweating, effectively reduces the burden of toxic metals as well. Sauna, described as a form of passive heat therapy typically hot and dry, above 100°F have been used for thousands of years rooted in Northern Europe. A systematic review showed that arsenic, cadmium, lead, and mercury were excreted in high concentrations in sweat especially compared to urine, highlighting the significance of such less invasive lifestyle measures in detoxification.[48] Sauna use has been deemed safe for most individuals with stable coronary artery disease, prior myocardial infarction, and up to class III congestive heart failure.[49] In fact, multi-session sauna use was associated with 40% reduction in all-cause mortality compared to less frequent users.[50] As a result of these detoxification practices, a positive impact on both mortality and aging has been suggested by previous literature see Table 2. Screening for

Table 2 Addressing Toxic Metals on CVD Risk

Species	Study Type	Subjects	Findings	Citation
Human	RCT	24	Consumption of probiotic yogurt had a protective effect against further increases in mercury and arsenic	Bisanz JE, Enos MK, Mwanga JR, Changalucha J, Burton JP, Gloor GB, Reid G. Randomized open-label pilot study of the influence of probiotics and the gut microbiome on toxic metal levels in Tanzanian pregnant women and school children. mBio. 2014 Oct 7;5(5): e01580–e01594. doi: 10.1128/mBio.01580–14. PMID: 25,293,764; PMCID: PMC4196227.[51]
Human	Meta analysis of RCT	1983	17 studies including 1 RCT, TACT, suggested improved outcomes which may provide more benefit to patients with diabetes and severe peripheral arterial disease	Ravalli F, Vela Parada X, Ujueta F, Pinotti R, Anstrom KJ, Lamas GA, Navas-Acien A. Chelation Therapy in Patients With metal toxicity and Cardiovascular Disease: A Systematic Review. J Am Heart Assoc. 2022 Mar 15;11(6):e024648. doi: 10.1161/ JAHA.121.024648. Epub 2022 Mar 1. PMID: 35,229,619; PMCID: PMC9075296.[52]

(*Continued*)

Table 2 (Continued).

Species	Study Type	Subjects	Findings	Citation
Human	Meta analysis	968	Sauna treatment LVEF, 6-min walk distance, and flow-mediated dilation increased along with BNP decrease	Li Z, Jiang W. Acute and short-term efficacy of sauna treatment on cardiovascular function: a meta-analysis: reply. Eur J Cardiovasc Nurs. 2021 Oct 27;20(7):730. doi: 10.1093/eurjcn/zvab050. PMID: 34,329,397.[53]
Human	Multi-arm RCT	47	Greater improvements in CRF, SBP, and Cholesterol were noted in Sauna intervention when compared to exercise alone.	Lee E, Kolunsarka I, Kostensalo J, Ahtiainen JP, Haapala EA, Willeit P, Kunutsor SK, Laukkanen JA. Effects of regular sauna bathing in conjunction with exercise on cardiovascular function: a multi-arm, randomized controlled trial. Am J Physiol Regul Integr Comp Physiol. 2022 Sep 1;323(3):R289-R299. doi: 10.1152/ajpregu.00076.2022. Epub 2022 Jul 4. PMID: 35,785,965; PMCID: PMC9394774.[54]

Abbreviations: CRF, Cardio Respiratory Fitness; SBP, Systolic Blood Pressure; LVEF, Left Ventricular Ejection Fraction; BNP, Brain Natriuretic Peptide.

metal exposure and its impact may have the potential to identify factors that can be affecting the aging process, these should encourage team science including Toxicologists and Functional Medicine specialists.

The Role of Estrogen in Cardiovascular Aging

There is known gender discrepancy related to treatment and prevention of CVD, particularly in women as they age.[55] Women over 60 are more likely to experience cardiovascular events compared to age-matched men due to loss of ovarian function and its protective effects.[56,57] Estrogens impact on vascular regrowth and endothelial dilation likely explain this. For decades estrogen replacement therapy has been found to have positive benefits for cardiovascular health per large studies[58] Controversy remains regarding the use of hormones hence continues to be an area of ongoing research. Studies support that Estradiol itself stimulates vascular endothelial integrity including replacement therapy shown to reduce progression of subclinical atherosclerosis.[59–61] Furthermore, hormone replacement therapy (HRT) users depending on the age and timing of use may experience less progression to CVD and mortality benefit.[62,63] As a result, recently years have seen the rise of HRT prescriptions across various medical disciplines. Further evidence refuting concerns about HRT and cancer point to Progestin's vs use of true Progesterone to be the cause.[64] Despite some studies revealing diminished mortality benefit from HRT in users beginning therapy beyond 10 years of menopause, this is primarily because estrogen may exacerbate already existing or CVD with age.[65,66] Personalized decision making and proper patient selection continues to be used to address this topic. The use of newer HRT modalities including transdermal and bioidentical hormone replacement (BHRT), has sparked a recent debate. BHRT involves the use of non-synthetic estradiol and progesterone, which closely mimic our own body's hormonal composition.[67] As these are often administered transdermally they have demonstrated less adverse effects when compared to oral synthetic hormone replacement due to bypassing the first-pass metabolism in the liver and its pro-thrombotic and inflammatory pathways.[68] Today the North American Menopause Society (NAMS) and The British Menopause Society support BHRT based on its mechanism of action and more recent data as a safe option for women to prevent CVD events.[69,70] Such an approach has the potential to provide many benefits including restore bone mineral density and minimize medication overuse see Table 3. As medical error including medications contribute to the third cause of death in America today, this potential is critical for constant review.[71,72] Estrogen's benefits are not exclusive to women. Studies have shown an inverse relationship between estradiol levels and CVD, emphasizing its importance in hormonal decline for both genders.[73] In men, declining estrogen levels often indicate testosterone deficiency as testosterone converts to estradiol. Studies using estradiol in men over the age of 65 interestingly have shown reductions in homocysteine, fibrinogen, and plasminogen activator inhibitor levels, along with improvements in lipid profiles.[74] Conventional practice guidelines still remain void of hormonal recommendations therefore studies to help provide guidance towards improvement in cardiovascular health are still needed.

Table 3 Transdermal Hormone Replacement on CVD Risk

Species	Study Type	Subjects	Findings	Citation
Human	RCT	172	TE + IMP tended to improve cardiac autonomic control and prevented age-related changes in endothelial function in postmenopausal women.	Gordon JL, Rubinow DR, Watkins L, Hinderliter AL, Caughey MC, Girdler SS. The Effect of Perimenopausal Transdermal Estradiol and Micronized Progesterone on Markers of Risk for Arterial Disease. J Clin Endocrinol Metab. 2020 May 1;105(5):e2050–60. doi: 10.1210/clinem/dgz262. PMID: 31,838,497; PMCID: PMC7096310.[75]
Human	Randomized pilot trial	57	MP + t-E2 demonstrated a positive effect on traditional CVD markers cardiac output, reduction in diastolic blood pressure, and total peripheral resistance after 12 months	Mittal et al. Impact of micronised progesterone and medroxyprogesterone acetate in combination with transdermal oestradiol on cardiovascular markers in women diagnosed with premature ovarian insufficiency or an early menopause: a randomised pilot trial. Maturitas. 2022.[76]
Human	RCT	596	HT with estradiol plus topical progesterone reduced atherogenic progression of arterial wall composition in healthy postmenopausal women who were within 6 years from menopause	Karim R, Xu W, Kono N, Sriprasert I, Li Y, Yan M, Stanczyk FZ, Shoupe D, Mack WJ, Hodis HN. Effect of menopausal hormone therapy on arterial wall echomorphology: Results from the Early versus Late Intervention Trial with Estradiol (ELITE). Maturitas. 2022 Aug;162:15–22. doi: 10.1016/j.maturitas.2022.02.007. Epub 2022 Mar 17. PMID: 35,474,254; PMCID: PMC9232990.[77]
Human	RCT	5359	Transdermal HRT had a positive effect on flow-mediated dilatation trend towards benefit in non-fatal M.I.	Bontempo S, Yeganeh L, Giri R, Vincent AJ. Use of MHT in women with cardiovascular disease: a systematic review and meta-analysis. Climacteric. 2024 Feb;27(1):93–103. doi: 10.1080/13,697,137.2023.2273524. Epub 2024 Jan 15. PMID: 37,933,495.[78]

Abbreviations: RCT, Randomized Controlled Trial; MP, Micronized Progesterone; t-E2, Transdermal Estradiol; HT, hormone Therapy; TE, Transdermal Estradiol; IMP, Intermitent Micronized Progesterone; M.I, Myocardial Infarction.

Nutraceuticals and Cardiovascular Aging

Nutraceuticals are product derived from food sources with potential health benefits in addition to the basic nutritional values. Some of these supplements available may have a potential benefit in cardiovascular health and aging. Nitric oxide (NO), for example, plays a crucial role in cardiovascular health by promoting vasodilation and protecting endothelial integrity.[79] Endogenous NO production significantly decreases by the age of 40, highlighting the need for adequate support to promote healthy aging and CVD progression.[80] Accumulation of asymmetric dimethylarginine (ADMA), resulting from exposure to ROS, may further impair NO production accelerating endothelial dysfunction and downstream cardiovascular complications.[81] Lifestyle factors, such as Ramadan-style eating habits, have shown to improve NO bioavailability, highlighting the possibility of interventions in this area of lifestyle medicine.[82] Nutraceuticals that enhance NO bioavailability, like L-citrulline and sodium nitrite, have shown promise in correcting age-related hypertension and endothelial damage.[83] Medications like phosphodiesterase inhibitors (PDE5i) show benefits in reducing mortality in patients after myocardial infarction through similar pathways of NO production making this a very exciting area of future research.[84,85] Resveratrol (RES) and Berberine are two additional nutraceuticals which offer potential as found to attenuate TMAO-induced atherosclerosis.[86] RES, a stilbene-based polyphenol, has further shown to improve lipid profiles, dysglycemia, and circulatory function, reducing conventional inflammatory risk factors and increasing endothelial NOS.[87,88] In a randomized controlled trial, a standardized dose of 300 mg of RES demonstrated improvement

in brachial flow-mediated dilation, without major adverse events reported in meta-analyses.[89] Curcumin is another well-documented nutraceutical with health benefits, including cardiovascular protection.[90] Derived from Indian turmeric, curcumin, the active ingredient, exhibits strong inhibitory effects on NF-kB and interleukin 6, which are markers of CVD progression as well.[91] It also activates SIRT1 genes, contributing to its anti-senescent properties. Studies have demonstrated positive effects of curcumin on central arterial hemodynamics and endothelial function among postmenopausal women, who are at higher risk for CVD compared to their male counterparts.[92,93] Curcumin has also been effective in preventing progression to overt diabetes in a placebo-controlled trial, with a low daily dose of just 0.5mg, highlighting its anti-aging capabilities.[94] A recent meta-analysis has confirmed the safety of curcumin at doses ranging from 80 mg to 4 grams, showing successful reduction of oxidative stress and subsequent inflammatory disease progression.[95] Combining Curcumin and RES appears to have safe and potentially synergistic effects on the inflammatory cascade as and therefore warrants further large scale studies to see if it can drastically improve conservative treatment.[96]

Conclusion

The aging population is facing a growing burden of age-related chronic diseases and most recently a decreased life expectancy, particularly from CVD. Conventional approaches still only focus on traditional risk factors overlooking crucial factors related to aging that have more recently have been supported. The systems biology inclusive of addressing the microbiome as well as environmental factors and age related hormonal decline in a systematic manner has the potential to address additional factors that contribute to CVD. It has already been shown to enhance quality of life measures compared to conventional care among patients part of Functional Medicine practices according to a 2019 publication in JAMA. Overall, addressing these missing links of aging and tailoring treatment to the individual necessitates a more holistic approach. Integrating these factors may lead to earlier assessment of cardiovascular risk, disease prevention, and potential reversal of age-related disease on the cardiovascular system. Collaboration between specialties, including Functional and Integrative Medicine, can further optimize care outcomes as a result and improve cardiovascular health for our aging population. The future perspective lies in further research to refine these approaches, identifying mortality benefits compared to controls, and optimizing patient care and longevity.

Disclosure

The authors report no conflicts of interest in this work.

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