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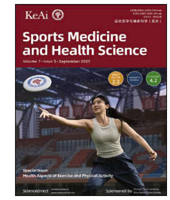

Editorial

Two-legged medicine: Exercise-mediated health benefits

1. Introduction

There is abundant evidence that the amount of habitual physical activity (PA) and the level of cardiorespiratory fitness (CRF) are inversely related to developing chronic diseases, including cardiovascular (CV) disease (CVD). Relative to the CV and all-cause mortality reductions associated with exercise, intensity and duration also appear to be inversely related. For example, the mortality reductions that are associated with a regular 5-min run ~ a 15-min walk, and a 25-min run ~ a 105-min walk.[1] In addition, at comparable levels of total energy expenditure, vigorous exercise seems to be more effective than moderate-intensity exercise in reducing CV risk.[2] Vigorous exercise training is also more effective than moderate intensity training at increasing CRF, expressed as metabolic equivalents or METs, which has been shown to confer a lower risk of mortality.[3] Accordingly, the optimal physiologic, clinical, and survival benefits of exercise are most likely to be achieved by progressing from moderate intensity exercise (usually defined as 40%–59% of functional capacity or 55%–69% of the maximal heart rate) to vigorous training regimens, corresponding to ≥ 60% of functional capacity or 70%–89% of the measured maximal heart rate.

This opening editorial to this special issue of the journal briefly reviews the related impact of PA and CRF on health outcomes and survival, with specific reference to terminology, epidemiologic studies, and potential underlying mechanisms, resistance training (RT), exercise preconditioning, heart failure (HF), and cancer. Related topics include childhood PA, dehydration, exerkines, sarcopenia, immediate cardioprotective effects of exercise training on acute myocardial infarction (AMI), the impact of CRF and/or obesity on HF survival and incidence, and the role of PA and CRF in cancer prevention and treatment as well as the value of RT in mitigating cancer-induced cachexia. Finally, we highlight the differential effects of exercise training on metabolic syndrome.

2. Physical activity and fitness terminology

In the context of this special issue, it is important to define commonly used terminology, with specific reference to PA, structured exercise, and CRF.[4] Physical activity is synonymous with bodily movement resulting from the contraction of skeletal muscle that increases energy expenditure above the resting level which is defined as 1 MET or 3.5 mL of oxygen per kilogram of body weight per minute or $mL{\cdot}kg^{-1}{\cdot}min^{-1}$. Accordingly, the intensity of PA is typically expressed as multiples of the resting metabolic rate or as METs. For example, running at 6 mph ~10 METs or 35 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$.

Exercise represents a subcategory of PA that is planned, structured, repetitive, and for the purpose of maintaining or increasing CRF, health, athletic performance, or combinations thereof. Cardiorespiratory fitness is defined as the capacity of the CV and respiratory systems to supply oxygen to the working skeletal muscles during peak or maximal levels of PA. It is typically estimated or measured directly during the final minute of the highest attained workload during progressive exercise testing and expressed as $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ or METs. This measure of physical performance is also commonly referred to as exercise capacity, functional capacity, aerobic capacity, or peak or maximal oxygen consumption. Importantly, PA and structured exercise are considered health behaviors, whereas CRF is a health outcome of these behaviors, which also has a genetic determinant.

The above-referenced terms have particular relevance to two of the outstanding contributions to this special issue of *Sports Med Health Sci.* Pfeiffer and Clevenger[5] discuss the modulators of early childhood PA participation as an important time to establish a lifelong active lifestyle, which, from a socioecological perspective, has implications for attenuating the development of chronic disease in young and middle-aged adults. Millard-Stafford et al. (https://doi.org/10.1016/j.smhs.2024.12.001), focus on factors influencing PA in warm-to-hot environments, including the negative impact of dehydration on physical performance, and the increasing number of hydration-related products, with specific reference to the optimal fluid formula during exercise.

3. Epidemiologic studies

In an early meta-analysis of 43 studies of the relation between PA and coronary heart disease (CHD) incidence, the relative risk of CHD in relation to physical inactivity ranged from 1.5 to 2.4, with a median value of 1.9.[6] Moreover, the relative risk of a sedentary lifestyle appeared to be similar in magnitude to that associated with other major CHD risk factors. Another systematic review and meta-analysis of 33 PA studies including 883 372 participants, reported pooled risk reductions of ~ (34% ± 1%) for CVD and all-cause mortality among the most physically active cohorts.[7] More recently, researchers estimated that the influence of 5 low-risk lifestyle factors (never smoking, body mass index [BMI] of 18.5–24.9 $kg{\cdot}m^{-2}$, ≥ 30 min per day of moderate-to-vigorous PA, moderate alcohol intake, and a healthy diet score [upper 40%]) on premature mortality and life expectancy in the U.S. population.[8] During the follow-up period, which extended up to 34 years for some participants, the most physically active cohorts of men and women (≥ 5.5 h/week) demonstrated 7-to 8-year gains in life expectancy.

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List of abbreviations

AMI	acute myocardial infarction
BMI	body mass index
CHD	coronary heart disease
CRF	cardiorespiratory fitness
CV	cardiovascular
CVD	cardiovascular disease
HF	heart failure
METs	metabolic equivalents
PA	physical activity
RT	resistance training

3.1. Potential beneficial underlying mechanisms

Regular moderate-to-vigorous PA, structured exercise, or both can decrease the risk of initial or recurrent CV events, presumably from multiple mechanisms, including anti-atherosclerotic, anti-ischemic, anti-arrhythmic, anti-thrombotic, and psychological effects (Fig. 1).[9] There are also multiple mechanisms by which vigorous-intensity exercise training may be more effective than moderate exercise in reducing CV risk (Fig. 2).[10] In addition, exercise preconditioning,[11] as described elsewhere in this issue, offers a unique and undervalued non-pharmacologic approach to attenuate the impact of acute coronary syndromes (angina pectoris and/or AMI) by protecting the heart against threatening cardiac arrhythmias, ventricular stunning, and myocardial tissue death.

In this issue of the journal, Powers et al.,[12] also extend these earlier reports on the health benefits of moderate-to-vigorous PA by identifying PA-induced mechanisms responsible for these favorable adaptations, which have led to the discovery of *exerkines*. These are specific molecules released into the bloodstream during exercise that influence specific tissues via autocrine, paracrine, and endocrine signaling. The authors suggest that these responses, in aggregate, may reduce the risk of chronic disease and all-cause mortality by clarifying the modes, intensities, and volume of exercise required to optimize health benefits in people with and without chronic disease.

4. Resistance training

In this issue of the journal, Jackson (https://doi.org/10.1016/j.smhs.2025.02.002) emphasized that aging of skeletal muscle is characterized by muscle weakness and decreased contractile force, secondary to sarcopenia, which has a profound negative impact on the quality of life of older people. Fortunately, resistance traing (RT) and some weight-bearing calisthenics are the only interventions known to reliably reduce muscle loss and weakness in the elderly, which may also attenuate age-related adverse neuromuscular changes over time. As Kraemer et al.,[13] point out, the benefits of RT apply not only to men, but women as well.

Resistance training, especially as an adjunct to endurance exercise programs, can provide an effective method for increasing muscle strength and endurance, preventing and managing a variety of chronic medical conditions, favorably modifying selected coronary risk factors, and enhancing psychosocial well-being.[14] In fact, studies suggest that it is comparable or superior to aerobic or endurance training in improving blood pressure, lipids/lipoproteins, and body composition (lean mass), as well as enhancing bone mineral density, insulin sensitivity, and basal metabolic rate.[15] Resistance training has also been shown to decrease the rate-pressure product when any given load is lifted, which may reduce cardiac demands during daily activities such as carrying packages or lifting moderate-to-heavy objects.[16,17] There is also intriguing data to suggest that grip strength is directly related to long-term survival.[18] Although the traditional weight-training prescription has involved performing each exercise three times (e.g., 3 sets of 10–15 repetitions per set), it appears that even 1 set provides improvements in muscular strength and endurance, at least for the novice exerciser.[15]

5. Exercise preconditioning

Increased levels of PA before hospitalization for suspected acute coronary syndrome appear to confer more favorable short-term outcomes, presumably due, at least in part, to a phenomenon known as exercise preconditioning.[11,19]

In a classic study involving 2 172 patients (average age, 66 years; 76% men) hospitalized for chest pain, the most physically active cohort showed much lower odds of in-hospital mortality or experiencing recurrent cardiac events within the first 30 days of hospital discharge,

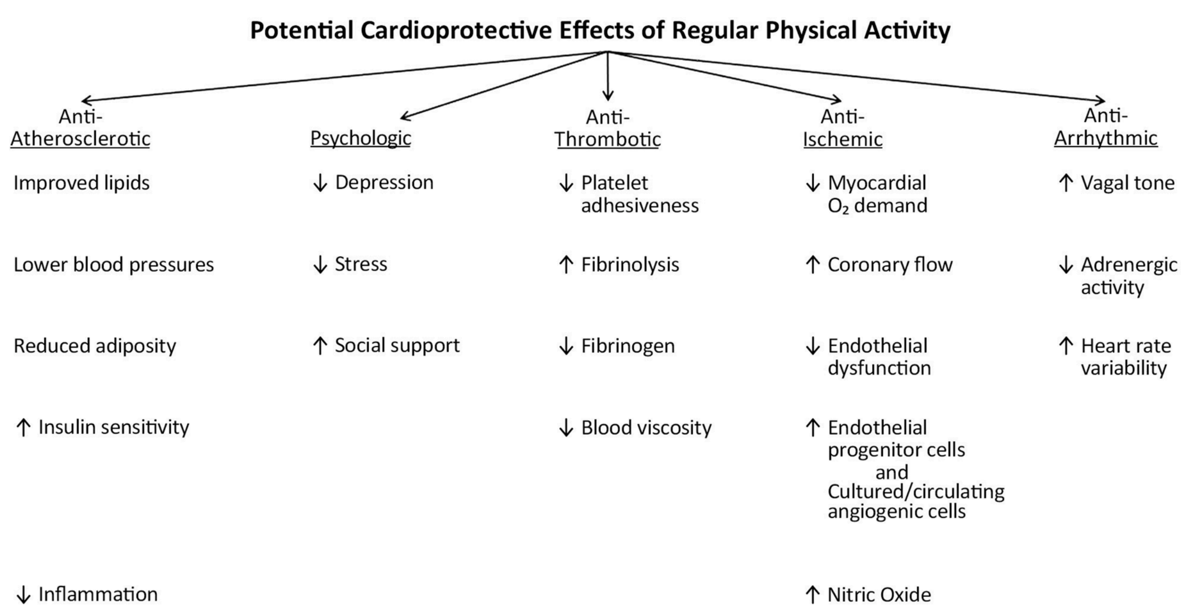

Fig. 1. An endurance (aerobic) exercise program sufficient to maintain and enhance cardiorespiratory fitness may provide multiple mechanisms to reduce nonfatal and fatal CV events. BP = blood pressure, CACs = cultured angiogenic cells, EPCs = endothelial progenitor cells, HR = heart rate, O_2 = oxygen. Arrows signify increased or decreased.

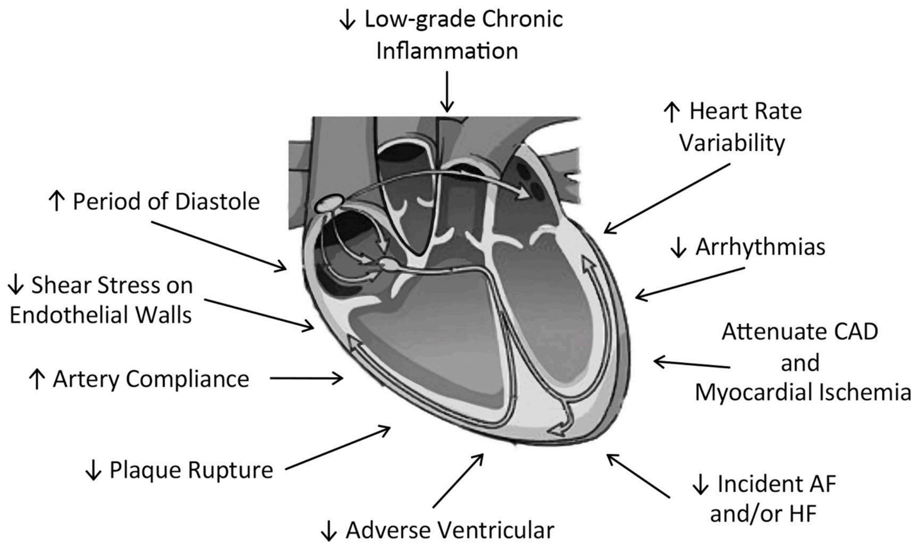

Fig. 2. In addition to decreases in sympathetic stimulation and increases in parasympathetic tone, multiple mechanisms by which vigorous – intensity exercise training may be more effective than moderate - intensity exercise at reducing CV risk. AF = atrial fibrillation, HF = heart failure, CAD = coronary artery disease. Adapted from reference[10].

corresponding to odds ratios of 0.56 and 0.80, respectively.[20] First described decades ago in animal studies, recent clinical investigations indicate that just 1 to 3 bouts of moderate intensity exercise appear to partially protect the human heart in response to an AMI.[19] In other words, the initiation of an exercise program seems to reduce the magnitude of associated cardiac arrhythmias, ventricular impairment, and myocardial tissue death. Moreover, the protective effects persist for several days to more than a week after the last 20-30-min exercise session.[11] Particularly encouraging is that the protective benefits of exercise preconditioning can be rapidly evoked, regardless of past levels of sedentary behavior or CRF and extend indefinitely for those individuals who continue to engage in moderate-intensity exercise on a regular basis.

The current review by Quindry and Michalak[21] in this issue of the journal, beautifully details and explains this cardioprotective mechanism, with specific reference to future scientific advances to better understand the most rapid and effective treatments to attenuate or even mitigate the physiologic and clinical consequences of AMI.

6. Heart failure

Heart Failure (HF) for individuals $\geq$ 65 years of age, including patients with reduced as well as preserved ejection fraction, represents a common cause of mortality and the most frequent cause of hospitalization in the U.S. and many developed countries. In this issue of the journal, LaMonte (https://doi.org/10.1016/j.smhs.2025.07.005) provides an enlightening overview regarding the impact of exercise on the 21st century epidemic of HF.

In an early widely-cited investigation, Mancini et al.,[22] evaluated whether direct measurement of exercise capacity, expressed as peak $\dot{V}O_2$ (mL·kg^{-1}·min^{-1} or as METs), can be used to predict survival in ambulatory patients (n = 122) with systolic HF (mean ± *SD* age = [50 ± 11] years; 84% men; mean ± *SD* ejection = [19% ± 7%]). HF patients with an exercise capacity > 14 mL·kg^{-1}·min^{-1} (> 4 METs) had cumulative 1-and 2-year survival rates of 94% and 84%, respectively. These survival rates are comparable, if not better than, survival achieved with cardiac transplantation. Moreover, those HF patients with an exercise capacity > 18 mL·kg^{-1}·min^{-1} (> 5 METs) demonstrated 100% survival at 1-year follow-up, highlighting the strong prognostic significance of this level of CRF in patients with severe left ventricular dysfunction.

In recent years, the impact of excess weight (obesity) has been shown to be associated with the risk of developing chronic diseases, including HF. On the other hand, numerous studies have also shown that higher levels of CRF prevent the development of chronic diseases. Two obvious questions arise: Can increased fitness levels neutralize the adverse effects of obesity? And, does the "obesity paradox" apply to the patient with CVD and HF?

Previously, we evaluated CRF and BMI in > 20 000 U S. male veterans (mean age = 58.0 years) who completed a maximal treadmill test within the previous 3 decades.[23] All had no evidence of myocardial ischemia or HF prior to exercise testing. CRF was estimated by the workload achieved during progressive treadmill testing and classified based on age-stratified quartiles of peak METs (least-fit, low-fit, moderate-fit, and high-fit), and BMI as: normal weight, overweight, and obese. During a median follow-up of 13.4 years, there were 2 979 HF events. Results indicated that, regardless of BMI, individuals with low CRF were more likely to develop HF in their later years. Accordingly, we concluded that when it comes to HF, it's better to be overweight/obese and fit, than normal weight and unfit.

To address the second question, a recent report showed that patients with HF and a BMI in the overweight or mild-to-moderate obesity ranges have better survival rates than do their underweight or normal weight counterparts. These data and other reports suggest that the "obesity paradox" persists in patients with CVD and HF.[24] However, this phenomenon only seems to be present in those with poor levels of CRF, whereas in those with relatively good CRF, prognosis is excellent, regardless of their BMI.

Finally, walking speed is a commonly used objective measure of resilience and functional capacity in older people, with or without known CVD, predicting survival in several cohort studies.[25] In outpatients with stable CVD, the 6-min walk test has been shown to provide independent and additive information beyond traditional coronary risk factors and a discrimination ability similar to aerobic capacity (peak METs) for predicting CV events, including HF, myocardial infarction, and death.[26] In another study of adults $\geq$ 65 years with HF, impairment in gait speed (< 0.8 m·s^{-1} *vs.* $\geq$ 0.8 m·s^{-1}), measured within 1 year before the diagnosis of incident HF, was independently associated with mortality (hazard ratio, 1.37), after adjusting for potential confounders.[27] Nevertheless, clinical trials are needed before we can confidently state that increasing walking speed will improve outcomes in the HF population.

7. Cancer

Physical activity and improved levels of CRF also appear to play important roles in the prevention and treatment of cancer. In an analysis of > 1.4 million individuals, higher levels of leisure-time PA were associated with a lower risk of half the cancers evaluated.[28] Similarly, two additional independent scientific reviews concluded that there is strong evidence to support the benefits of regular PA in the prevention of certain cancers, including breast, colon, endometrial, kidney, bladder, esophageal, and stomach.[29,30]

In another sobering systematic review that included 71 654 individuals with diagnosed cancer and 2002 cancer-related deaths, patients with the highest levels of CRF had nearly a 50% reduced risk of cancer mortality compared with their counterparts with the lowest fitness.[31] Collectively, the above-referenced findings suggest that regular moderate-to-vigorous PA ($\geq$ 3 METs) and increased CRF are associated with reduced cancer risk and better survival outcomes among individuals diagnosed with cancer. These data and the enlightening systematic review by Horawski et al.,[32] published in this issue of the journal, highlighting the role of RT in mitigating cancer-induced cachexia, the involuntary loss of lean body mass and adipose tissue that occur in up to 80% of all cancer patients, substantiate the salutary impact of exercise training in every individual's cancer care plan.

8. Conclusions

In summary, higher levels of PA and age/sex – adjusted CRF are associated with a reduced risk of developing hypertension, obesity, type 2 diabetes, metabolic syndrome, atrial fibrillation, chronic kidney disease, HF, and major CV events, including myocardial infarction, coronary artery bypass graft surgery, stroke, and sudden cardiac death.[33] With respect to metabolic syndrome, Moseley et al. (https://doi.org/10.1016/j.smhs.2025.03.006), in this issue of the journal, reported a relationship between exercise energy expenditure and improvements in composite measures of metabolic syndrome, which appear closely linked to insulin sensitivity. The authors concluded that combined aerobic and RT interventions offer the most robust improvements for composite metabolic syndrome, as compared with either training mode alone.

Relative to CVD, the inverse association of lower incidence of type 2 diabetes with PA or CRF also applies to the diabetogenic effects of cholesterol–lowering statins. These findings suggest that regular moderate-to-vigorous PA appears to more than compensate for the purported modest increase in diabetes risk from statin use.[9,33] Finally, in a study of > 10 000 veterans with dyslipidemia over a 10-year follow-up, investigators reported that the cohort on statin therapy with high CRF had substantially lower mortality risk (~3.0-fold) than their low fit counterparts taking statins.[34] These results reinforce the importance of PA/CRF as adjunctive therapy for individuals with dyslipidemia.

In closing, a just-published Finnish twin study concluded that the beneficial association of long-term leisure-time PA, specifically, the anti-aging and reduced mortality effects, were largely accounted for by other health-related factors, including genetic confounding and reverse causality.[35] However, the methodologic assumptions put forth, multilevel survival models employed, and the inferences regarding statistical treatment of the data, represented potential study limitations, rendering the conclusions tenuous at best. Accordingly, the author's interpretation of their findings have already been vigorously challenged. The fact of the matter is that overwhelming data have previously substantiated the health benefits of regular, moderate-to-vigorous exercise.[33] Perhaps the late William C. Roberts, MD, the former editor of the American Journal of Cardiology, summed it up best when he described the medicinal properties of exercise as "an agent with lipid-lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic, and anti-depressive qualities."[36]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet*. 2011; 378(9798):1244–1253. https://doi.org/10.1016/S0140-6736(11)60749-6.
2. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. *Am J Cardiol*. 2006;97(1):141–147. https://doi.org/10.1016/j.amjcard.2005.07.130.
3. Swain DP, Franklin BA. VO_2 reserve and the minimal intensity for improving cardiorespiratory fitness. *Med Sci Sports Exerc*. 2002;34(1):152–157. https://doi.org/10.1097/00005768-200201000-00023.
4. Franklin BA, Thompson PD, Al-Zaiti SS, et al. Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training; placing the risks into perspective-an update: a scientific statement from the American Heart Association. *Circulation*. 2020;141(13):e705–e736. https://doi.org/10.1161/CIR.0000000000000749.
5. Pfeiffer KA, Clevenger KA. Importance, unique aspects and guidelines, and building blocks of early childhood physical activity from a socioecological perspective. *Sports Med Health Sci*. 2025;7(5):308–316. https://doi.org/10.1016/j.smhs.2025.01.004.
6. Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. *Annu Rev Publ Health*. 1987;8:253–287. https://doi.org/10.1146/annurev.pu.08.050187.001345.
7. Nocon M, Hiemann T, Müller-Riemenschneider, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systemic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil*. 2008;15(3):239–246. https://doi.org/10.1097/HJR.0b013e3282f55e09.
8. Li Y, Pan A, Wang DD, et al. Impact of healthy lifestyle factors on life expectancies in the US population. *Circulation*. 2018;138(4):345–355. https://doi.org/10.1161/CIRCULATIONAHA.117.032047.
9. Franklin BA, Quindry JC. Biochemistry of exercise training and mitigation of cardiovascular disease. In: Tidus P, MacPheroson R, Leblanc PJ, eds. *Biochemistry of Exercise*. Rutledge Publishers; 2021.
10. Franklin BA, Kaminsky LA, Kokkinos P. Quantitating the dose of physical activity in secondary prevention: relation of exercise intensity to survival. *Mayo Clin Proc*. 2018;93(9):1158–1163. https://doi.org/10.1016/j.mayocp.2018.07.014.
11. Quindry JC, Franklin BA. Exercise preconditioning as a cardioprotective phenotype. *Am J Cardiol*. 2021;148:8–15. https://doi.org/10.1016/j.amjcard.2021.02.030.
12. Powers SK, Goldstein E, Lategan-Potgieter R, Schrager M, Skelton M, Demirel H. Health benefits of physical activity: what role does skeletal muscle-organ crosstalk play? *Sports Med Health Sci*. 2025;7(5):329–340. https://doi.org/10.1016/j.smhs.2025.02.010.
13. Kraemer WJ, Fragala MS, Ratamess NA. Evolution of resistance training in women: history and mechanisms for health and performance. *Sports Med Health Sci*. 2025;7(5):351–365. https://doi.org/10.1016/j.smhs.2025.01.005.
14. Paluch AE, Boyer WR, Franklin BA, et al. Resistance exercise training in individuals with and without cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2024;149:e217–e231. https://doi.org/10.1161/CIR.0000000000001189.
15. Williams MA, Haskell WL, Ades PA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association. *Circulation*. 2007;116:572–584. https://doi.org/10.1161/CIRCULATIONAHA.107.185214.
16. McCartney N, McKelvie RS, Martin J, Sale DG, MacDougall JD. Weight-training-induced attenuation of the circulatory response of older males to weight lifting. *J Appl Physiol (1985)*. 1993;74:1056–1060. https://doi.org/10.1152/jappl.1993.74.3.1056.
17. Grafe K, Bendick P, Burr M, Boura J, Franklin BA. Effects of resistance training on vascular and hemodynamic responses in patients with coronary artery disease. *Res Q Exerc Sport*. 2018;89(4):457–464. https://doi.org/10.1080/02701367.2018.1519385.
18. Sayer AA, Kirkwood TB. Grip strength and mortality: a biomarker of ageing? *Lancet*. 2015;386(9990):226–227. https://doi.org/10.1016/S0140-6736(14)62349-7.
19. Thijssen DHJ, Redington A, George KP, Hopman MTE, Jones H. Association of exercise preconditioning with immediate cardioprotection: a review. *JAMA Cardiol*. 2018;3:169–176. https://doi.org/10.1001/jamacardio.2017.4495.
20. Pitsavos C, Kavouras SA, Panagiotakos DB, et al. Physical activity status and acute coronary syndromes survival the GREECS (Greek study of acute coronary syndromes) study. *J Am Coll Cardiol*. 2008;51:2034–2039. https://doi.org/10.1016/j.jacc.2008.01.053.

21. Quindry J, Michalak RE. Exercise induced cardioprotection: from endogenous to exogenous mechanisms. *Sports Med Health Sci*. 2025;7(5):366–374. https://doi.org/10.1016/j.smhs.2025.03.009.
22. Mancini DM, Eisen H, Kussamaul W, Mull R, Edmunds JrLH, Wilson JR. Value of peak exercise oxygen for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83:778–786. https://doi.org/10.1161/01.cir.83.3.778.
23. Kokkinos P, Faselis C, Franklin B, et al. Cardiorespiratory fitness, body mass index and heart failure incidence. *Eur J Heart Fail*. 2019;4:436–444. https://doi.org/10.1002/ejhf.1433.
24. Lavie CJ, Kokkinos P, Lin GM. Obesity paradox is still alive in heart failure. *Heart*. 2023;109(20):1506–1507. https://doi.org/10.1136/heartjnl-2023-322797.
25. Franklin BA, Brinks J, Sacks R, Trivax J, Friedman H. Reduced walking speed and distance as harbingers of the approaching grim reaper. *Am J Cardiol*. 2015;116: 313–317. https://doi.org/10.1016/j.amjcard.2015.04.024.
26. Beatty AL, Schiller NB, Whooley MA. Six-minute walk test as a prognostic tool in stable coronary heart disease. Data from the heart and soul study. *Arch Intern Med*. 2012;172:1096–1102. https://doi.org/10.1001/archinternmed.2012.2198.
27. Lo AX, Donnelly JP, McGwin Jr G, Bittner V, Ahmed A, Brown CJ. Impact of gait speed and instrumental activities of daily living on all-cause mortality in adults $\geq$ 65 years with heart failure. *Am J Cardiol*. 2015;115:797–801. https://doi.org/10.1016/j.amjcard.2014.12.044.
28. Moore SC, Lee IM, Weiderpass E, et al. Association if leisure time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176(6): 816–825. https://doi.org/10.1001/jamainternmed.2016.1548.
29. 2018 Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. Washington, DC: US Department of Health and Human Services; 2018.
30. Patel AV, Friedenreich CM, Moore SC, et al. American college of sports medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. *Med Sci Sports Exerc*. 2019;51(11):2391–2402. https://doi.org/10.1249/MSS.0000000000002117.
31. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol*. 2015;26(2):272–278. https://doi.org/10.1093/annonc/mdu250.
32. Horawski JL, Fleszar-Pavlovic SE, Lopez-Pentecost M, et al. The role of resistance training in mitigating cancer-induced cachexia: a systemic review. *Sports Med Health Sci*. 2025;7(5):384–392. https://doi.org/10.1016/j.smhs.2025.01.002.
33. Kokkinos P, Narayan P, Myers J, Franklin B. Cardiorespiratory fitness and the incidence of chronic disease. *J Clin Exerc Physiol*. 2018;7(2):37–45. https://doi.org/10.31189/2165-6193-7.2.37.
34. Kokkinos P, Faselis C, Myers J, et al. Interactive effects of fitness and Statin treatment on mortality risk in veterans with dyslipidemia: a cohort study. *Lancet*. 2013; 381:394–399. https://doi.org/10.1016/S0140-6736(12)61426-3.
35. Kankaanpää A, Tolvanen A, Joesuu L, et al. The associations of long-term physical activity in adulthood with later biological aging and all-cause mortality-a prospective twin study. *Eur J Epidemiol*. 2025;40:107–122. https://doi.org/10.1007/s10654-024-01200-x.
36. Robert WC. An agent with lipid-lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic and antidepressive qualities. *Am J Cardiol*. 1984;53(1):261–262. https://doi.org/10.1016/0002-9149(84)90725-2.

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