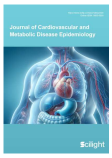
Scilight

Journal of Cardiovascular and Metabolic Disease Epidemiology

https://www.sciltp.com/journals/jcmde



Mini Review

Current Concepts on Cardiorespiratory Fitness, and Health Outcomes: A Brief Review

Peter Kokkinos [1,2]

[1] Department of Kinesiology and Health 70 Lipman Drive, Rutgers University, New Brunswick, NJ 08901, USA; peter.kokkinos@va.gov

[2] Veterans Affairs Medical Center, Washington, DC 20422, USA

How To Cite: Kokkinos, P. Current Concepts on Cardiorespiratory Fitness, and Health Outcomes: A Brief Review. *Journal of Cardiovascular and Metabolic Disease Epidemiology* **2025**, *1*(1), 2.

Received: 16 November 2024
Revised: 09 March 2025
Accepted: 10 March 2025
Published: 14 March 2025

Abstract: The link between a physically active lifestyle and human health, first described by Hippocrates, was scientifically scrutinized for the last seven decades. The cumulative evidence from large and well-designed epidemiologic studies strongly supports a physically active lifestyle that leads to improved cardiorespiratory fitness (CRF) which confers significant health benefits across the age, gender, and race spectra. The health benefits are evident beyond an exercise volume threshold and increase progressively with higher exercise volumes and are independent of comorbidities. Specifically, increased CRF is strongly and inversely associated with the incidence of chronic cardiometabolic diseases, and the risk of premature mortality. In dyslipidemic populations, CRF is equally effective with statin therapy in lowering mortality risk. However, the combination of the two therapies (CRF and statin treatment) were more effective than either therapy alone. In non-diabetic patients the incidence of diabetes mellitus (T2DM) was amplified by obesity and statins and was attenuated by high CRF. In T2DM patients treated with statins the progression to insulin therapy (worsening of T2DM) was amplified by obesity and statins and was attenuated by high CRF. There is also evidence that excessive amounts of physical activity (work volume) are counterproductive and even harmful. The recommended exercise volume an intensity necessary for health benefits is relatively moderate and achievable by most middle-aged and older individuals engaging in such activities as brisk walk 30–50 min per day most days of the week. Nevertheless, exercise prescriptions should be personalized.

Keywords: physical activity; fitness; health outcomes

1. Introduction

The link between fitness and health outcomes was first introduced by Hippocrates approximately 2500 years ago. In his statements regarding fitness, disease and mortality Hippocrates makes it clear that the use of all parts of the body when used in moderation in tasks in which they are design to perform, become healthy and well developed and age slowly. However, if unused and left idle, they become liable to disease, defective in growth, and age quickly. In another statement Hippocrates states that "walking is a man's best medicine."

The unprecedented wisdom of these statements is not so much that exercise is beneficial, but that exercise is used "in moderation". For the first time, exercise intensity is proposed, and walking is introduced as the mode by which physical activity can be implemented in a large segment of the public. These concepts did not become obvious until a few decades ago, and for some, not even in current times. In the 1970s and 80s, the prevailing thinking was that improvements in CRF required exercising at high intensities with no regards of the potential risks posed by such exercise practices, and that those who could run marathons were immune to heart disease. It wasn't until a few exercise-related deaths, when we began to appreciate that at least too much exercise could potentially lead to a serious cardiac event and even death, especially in sedentary populations. The landmark studies by Professor Steven Blair reintroduced the concept proposed by Hippocrates that moderate intensity exercise (brisk walking) is adequate for beneficial health outcomes [1–3].

In more modern times, advances in computer power, data retrieval, storage, and analytical technics have resulted in a wealth of epidemiologic evidence that have solidified the role of exercise and other healthy lifestyle practices in the prevention and management of chronic disease. In 2022 the American Heart Association Advisory Presidential Advisory defined eight lifestyle modifications that included healthy diet, participation in physical activity, maintaining healthy body weight, avoidance of nicotine exposure, and healthy levels of blood pressure, blood lipids, blood glucose, and sleep health, to promote cardiovascular health (CVH) and shift the focus from disease treatment to disease prevention [4]. The main purpose of this construct named Life's Essential 8, is to provide a road map to measure, monitor, and improve a wide array of health outcomes and quality of life.

In all studies, a higher the number of ideal CVH factors was associated with a markedly lower risk for CVD events and all-cause mortality regardless of race and ethnicity or socioeconomic position. Potential mechanisms through which higher CVH is associated with lower CVD risk involve endothelial function, inflammation, atherosclerosis, cardiac remodeling, hemostatic factors, and epigenetics [5,6]. Furthermore, attempts to define potential pathways to explain the CVH status and clinical CVD events association suggests that the protection conferred by optimal CVH may be "more than the sum of its parts" [7]. This suggests that at least one of the components included in the Life's Essential 8 has a favorable modulatory effect on at least one other components, thus amplifying the health benefits beyond the expected sum of the components involved. Although this component is yet to be identified, cumulative evidence strongly suggests that this "super modulator" is increased physical activity that leads to improved cardiorespiratory fitness (CRF) defined as one's capacity to provide the necessary energy for sustained physical activity via aerobic pathways. CRF is assessed objectively by a standardized exercise treadmill test (ETT) and is expressed in Metabolic Equivalents (METs; 1 MET = 3.5 mL per kg of body weight per minute).

Despite the significant evolution for the past decades in our quest to define the CRF-health outcomes association, challenges persist. A better understand of the exercise volume necessary for favorable changes for different disease and across the age, race and sex spectra, cardiac adaptations associated with strength training, the risk associated with exercise in different populations, and the independent or synergistic effects of CRF and genetic factors on the CRF-health outcomes have not been fully addressed. The Journal of Cardiovascular and Metabolic Disease Epidemiology is devoting a section to explore the potential impact of lifestyle factors on human health.

2. Cardiorespiratory Fitness and the Incidence of Chronic Disease

For the past seven decades, evidence accumulated from a plethora of large and well-designed epidemiologic studies and randomized-controlled trials has shown that improved CRF has a favorable effect on blood pressure, cardiac function, endothelial function, glucose, and lipid metabolism, and body composition [8–13].

Findings also support that CRF measured objectively by a standardized exercise treadmill test (ETT) is inversely associated with the incidence and progression of chronic disease. In over 2300 pre-hypertensive individuals, we observed an inverse, S-shaped association between exercise capacity and the rate of progression from prehypertension to hypertension in middle-aged and older male veterans [14]. The protective effects of fitness were evident when exercise capacity exceeded 8.5 METs. Specifically, when compared to highly fit individuals (peak METs achieved >10.0), the rate of progression to hypertension was 36.0% higher for the moderately fit (8.6–10.0 METs), 66.0% higher for the Low-fit (6.6–8.5 METs) and 72.0% higher for those in lowest fitness category (≤6.5 METs).

CRF was also associated inversely with the incidence of diabetes mellitus (T2DM) and the rate of T2DM progression in dyslipidemic patients treated with statins compared to those not treated with statins [15,16]. Specifically, the statin-related increased risk of developing T2DM was 50% higher for patients in the lowest CRF category, and 22% higher for those in the low CRF category. For the Moderate-and High-Fit individuals, the risk was similar to those not treated with statins. For patients with T2DM, the statin-related rate of progression to insulin therapy (an indicator of worsening T2DM) was increased by relatively poor fitness and obesity. Conversely, the progression rate was mitigated by increased CRF regardless of body weight status [16].

3. CRF and Cardiovascular Disease

There is also strong epidemiologic evidence supporting an inverse association between CRF and the incidence of chronic heart failure (CHF) [17–19]. Conversely, increased adiposity as reflected by higher body mass index (BMI) levels is associated with increased incidence of HF [20,21]. To determine if CRF attenuates the deleterious impact of obesity on CHF, we assessed the interactive effect of CRF and BMI on the incidence of HF in >20,000 US male veterans [17]. CRF in this cohort was assessed objectively by a standardized exercise treadmill test. Compared to the individuals in the lowest CRF category (least fit), we observed a progressively lower HF risk with increased CRF within all BMI categories, after adjusting for all comorbidities. Specifically, for those with normal body weight (BMI 18.5–24.9 kg/m^2) HF risk was 28%, 54% and 63% lower for Low-fit, Moderate-fit and High-fit individuals, respectively. For overweight individuals (BMI 25.0–29.9 kg/m^2) the risk was 25% lower for Low-fit, individuals, 47%, and 66% lower for Moderate-fit and High-fit individuals. For obese individuals (BMI ≥ 30.0 kg/m^2) the risk 36%, 57% and 73% lower for the same CRF categories. These findings support an inverse and independent association between CRF and the risk of developing HF. Considerably lower HF risk was noted with even modest levels of CRF (peak METs for Low-fit 6.7 ± 1.3 and Moderate-fit 8.1 ± 1.1). The public health significance of these findings is that the physical activity requirements to potentially lower the incidence of HF are achievable by most middle-age and older individuals by engaging in moderate intensity physical activities, such as brisk walk for 30–50 min per session most days of the week [22].

In a much larger study of 667,730 US Veterans, we also assessed the incidence of HF with preserved ejection fraction (HFpEF) [23], a condition defined as having an ejection fraction ≥50% [24]. After adjusting for comorbidities, we noted that the risk of HFpEF decreased progressively across CRF categories as CRF increased. The HFpEF risk was 27% lower for the low-fit (METs 7.3 ± 1.4), 43% for moderate-fit (METs 8.6 ± 1.4), and 66% lower for individuals in the highest CRF category (METs 13.6 ± 1.8). There were also two unexpected findings. First, we noted that being unfit carried the highest risk (nearly 3.0 times higher) than any other comorbidity. However, change in CRF over time reflected reciprocal changes in the risk of HFpEF and that the risk of unfit individuals who improved their fitness status by approximately 3.0 METs was 37% lower compared to those who remained unfit [23].

Collectively, these findings strongly support that relatively low CRF carries a high risk of developing HFpEF, more so than several traditional clinical risk indicators. This risk is attenuated substantially if CRF is improved. This is yet another reason that regular physical activity should be promoted by healthcare professionals regardless of age or risk factors to attenuate the risk of developing HFpEF. Finally, the risk for major adverse cardiovascular events (MACE) was inversely associated with CRF independent of all other comorbidities for those <60 and ≥60 years of age. When an age-specific MET threshold was defined, the risk for MACE increased significantly for those below that threshold and decreased for those above it [25].

4. Cardiorespiratory Fitness, Physical Activity and Mortality

Accumulated evidence from large and well-conducted epidemiologic studies have led to an indisputable conclusion that improved CRF, as determined objectively by a maximal exercise test or a physically active lifestyle is inversely associated with the risk for cardiovascular and all-cause mortality in apparently healthy individuals [1–4,8,9] and in patients with comorbidities [8–12,26] and documented cardiovascular disease [27,28]. This association is robust, graded, and independent of known cardiovascular risk factors and other co-morbidities, it is similar for both males and females [29,30] and across the age, and race spectra [30]. When compared to the least fit individuals, the risk declined progressively across the CRF categories for all ages. The decline in risk ranged from approximately 25% to 80%, depending on the age group. Approximately 50% lower risk is evident at the peak exercise capacity of approximately 11.0 METs for those 30–49 years of age, and 10.0 METs, 9.0 METs, 8,0 METs, and 7.0 METs for those aged 50.0–59.0 years; 60.0–69.0; 70.0–79.0; and 80.0–95.0 [30]. The reduction in mortality risk for each one metabolic equivalent (1-MET) increase in exercise capacity ranges between 10% to 25%, with no substantial sex differences [13,31,32].

In a large study of 93,060 US Veterans with two exercise evaluations at least 1 year apart (mean 5.8 ± 3.7 years), we observed that changes in CRF reflected inverse and proportional changes in mortality risk for those with and without cardiovascular disease [29]. Specifically, improved CRF from baseline to the final exercise evaluation was associated by approximately 10% to 50% lower mortality risk. Conversely, a decline in CRF was associated with approximately 10% to 75% higher mortality risk. These findings suggest that the favorable health outcomes associated with CRF are independent of genetic factors [28]. They also support the hypothesis that participation in aerobic activities leads to structural and functional physiological adaptations and these adaptations render an individual more resistant to injury or disease, ultimately resulting in lower mortality rates independent of genetic factors.

It is also well-accepted that exercise intensity, duration, and volume threshold are necessary beyond which health benefits accumulate exponentially, before reaching a plateau (S-shaped curve association). Most of the health benefits are realized at relatively lower levels of physical activity once the threshold is overcome. Generally, exercise thresholds below 6 METs have been associated with higher mortality [1–3]. However, age is an important determinant of exercise capacity and when age is considered an optimal MET threshold for individuals <50 years of age is between 8 to 9 METs and declines by 1 MET per decade to a threshold between 5 to 6 METs for those ≥70 years [33]. Compared to the mortality risk of those with an exercise capacity within their age-specific threshold, the risk for those with exercise capacities 2.0 or more METs below their respective MET thresholds was approximately 30% to 80% higher. Conversely the mortality risk was 30% to 50% lower in those with exercise capacities 2.0 or more METs above the threshold.

There is also evidence of an independent and synergistic effects of CRF with medication in lowering the risk of mortality. In dyslipidemic patients treated with statins the mortality risk across CRF categories was inverse and graded. Compared to patients in the lowest CRF category (exercise capacity ≤5.0 METs), mortality risk in those with moderate CRF was 36% lower and declined progressively to 68% for patients in the highest CRF category. The strength of the association was similar in those not treated with statins (range 26% to 63% lower risk for same CRF categories). These findings suggest that CRF lowers risk independent of statins and that the combination of statin treatment and an exercise capacity of more than 5 MET lowers mortality risk substantially more than either alone [26].

Finally, there is evidence that excessive amounts of physical activity (work volume) are counterproductive and even harmful. The exercise volume threshold and the level of work at which exercise becomes counterproductive are both undoubtedly influenced by age, health, fitness status, and genetics, and a precise definition may be difficult. Therefore, exercise prescriptions should be personalized.

5. Conclusions

The plethora of evidence suggest that physical activity of adequate intensity, duration, and volume attenuates the development of chronic disease and premature mortality, regardless of age, race, or sex. The volume and intensity of the activity necessary for these health benefits is relatively moderate and achievable by most middle-aged and older individuals. It is well-accepted that ≥150 min of moderate-intensity exercise (brisk walking) or 75 min of high-intensity exercise (jogging) is adequate to promote the aforementioned. To achieve this one should engage in such activities (walking or jogging) 30–50 min per day, most days of the week [22].

Funding

This research received no external funding.

Conflicts of Interest

The author declares no conflict of interest.

References

1. Blair, S.N.; Kohl, H.W.; Paffenbarger, R.S.; et al. Physical fitness and all-cause mortality: A prospective study of healthy men and women. *JAMA* **1989**, *262*, 2395–2401.
2. Blair, S.N.; Kohl, H.W., III; Barlow, C.E.; et al. Changes in physical fitness and all-cause mortality: A prospective study of healthy and unhealthy men. *JAMA* **1995**, *273*, 1093–1098.
3. Blair, S.N.; Kampert, J.B.; Kohl, H.W., III; et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* **1996**, *276*, 205–210.
4. Lloyd-Jones, D.M.; Allen, N.B.; Anderson, C.A.; et al. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory from the American Heart Association. *Circulation* **2022**, *146*, e18–e43. https://doi.org/10.1161/CIR.0000000000001078.
5. Joyce, B.T.; Gao, T.; Zheng, Y.; et al. Epigenetic age acceleration reflects long-term cardiovascular health. *Circ. Res.* **2021**, *129*, 770–781. https://doi.org/10.1161/CIRCRESAHA.121.318965.
6. Pottinger, T.D.; Khan, S.S.; Zheng, Y.; et al. Association of cardiovascular health and epigenetic age acceleration. *Clin. Epigenetics* **2021**, *13*, 42. https://doi.org/10.1186/s13148-021-01028-2.
7. Lloyd-Jones, D.M. Cardiovascular health and protection against CVD: More than the sum of the parts? *Circulation* **2014**, *130*, 1671–1673. https://doi.org/10.1161/CIRCULATIONAHA.114.012869.
8. Ross, R.; Arena, R.; Myers, J.; et al. Update to the 2016 American Heart Association cardiorespiratory fitness statement. *Prog. Cardiovasc. Dis.* **2024**, *83*, 10–15.
9. Isatha, A.; Koziol, K.J.; Martinez, M.W.; et al. Exercise and cardiovascular health: A state-of-the-art review. *Prog. Progress. Cardiovasc. Dis.* **2023**, *79*, 44–52.
10. Kokkinos, P. Cardiorespiratory Fitness, Exercise, and Blood Pressure. *Hypertension* **2014**, *64*, 1160–1164.

11. Lavie, C.J.; Schutter, A.D.; Parto, P.; et al. Obesity and Prevalence of Cardiovascular Diseases and Prognosis-The Obesity Paradox Updated. *Prog. Progress. Cardiovasc. Dis.* **2016**, *58*, 537–547.
12. Laviel, C.J.; Ortega, F.B.; Kokkinos, P. Impact of Physical Activity and Fitness in Metabolically Healthy Obesity. *J. Am. Coll. Cardiol.* **2018**, *71*, 812–813.
13. Kokkinos, P.; Myers, J. Exercise and Physical Activity: Clinical Outcomes and Applications. *Circulation* **2010**, *112*, 1637–1648.
14. Faselis, C.; Doumas, M.; Kokkinos, J.P.; et al. Exercise capacity and progression from prehypertension to hypertension. *Hypertension* **2012**, *60*, 333–338.
15. Kokkinos, P.; Faselis, C.; Narayan, P.; et al. Cardiorespiratory Fitness and Incidence of Type 2 Diabetes in US Veterans on Statin Therapy. *Am. J. Med.* **2017**, *130*, 1192–1198. https://doi.org/10.1016/j.amjmed.2017.04.042.
16. Kokkinos, P.; Nylen, E.; Faselis, C.; et al. Progression to Insulin Therapy in Patients with Type 2 Diabetes According to Cardiorespiratory Fitness, Body Mass Index, and Statin Therapy. *Mayo Clin. Proc.* **2024**, *99*, 249–259.
17. Kokkinos, P.; Faselis, C.; Franklin, B.; et al. Cardiorespiratory fitness, body mass index and heart failure incidence. *Eur. J. Heart Fail.* **2019**, *21*, 436–444. https://doi.org/10.1002/ejhf.1433.
18. Jonathan, M.; Kokkinos, P.; Chan, K.; et al. Cardiorespiratory Fitness and Reclassification of Risk for Incidence of Heart Failure: The Veterans Exercise Testing Study. *Circ. Heart Fail.* **2017**, *10*, e003780. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003780.
19. Pandey, A.; Patel, K.V.; Vaduganathan, M.; et al. Physical activity, fitness, and obesity in heart failure with preserved ejection fraction. *JACC Heart Fail.* **2018**, *6*, 975–982.
20. Hales, C.M.; Carroll, M.D.; Fryar, C.D.; et al. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. *NCHS Data Brief* **2020**, *2020*, 1–8.
21. Lavie, C.J.; Alpert, M.A.; Arena, R.; et al. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail.* **2013**, *1*, 93–102.
22. Nelson, M.E.; Rejeski, W.J.; Blair, S.N.; et al. Physical activity and public health in older adults: Recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation* **2007**, *116*, 1094–1105. https://doi.org/10.1249/mss.0b013e3180616aa2.
23. Kokkinos, P.; Faselis, C.; Pittaras, A.; et al. Cardiorespiratory fitness, and risk of heart failure with preserved ejection fraction. *Eur. J. Heart Fail.* **2024**, *26*, 1163–1171. https://doi.org/10.1002/ejhf.3117.
24. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* **2022**, *145*, e895–e1032. https://doi.org/10.1161/CIR.0000000000001062.
25. Kokkinos, P.; Faselis, C.; Myers, J.; et al. Cardiorespiratory Fitness and Incidence of Major Adverse Cardiovascular Events in US Veterans: A Cohort Study. *Mayo Clin. Proc.* **2017**, *92*, 39–48.
26. Kokkinos, P.; Faselis, C.; Myers, J.; et al. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: A cohort study. *Lancet* **2013**, *381*, 394–399.
27. Myers, J.; Prakash, M.; Froelicher, V.; et al. Exercise capacity and mortality among men referred for exercise testing. *N. Engl. J. Med.* **2002**, *346*, 793–801.
28. Kokkinos, P.; Faselis, C.; Samuel, I.B.H.; et al. Changes in Cardiorespiratory Fitness and Survival in Patients with or without Cardiovascular Disease. *J. Am. Coll. Cardiol.* **2023**, *81*, 1137–1147.
29. Mandsager, K.; Harb, S.; Cremer, P.; et al. Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. *JAMA Netw. Open* **2018**, *1*, e183605.
30. Kokkinos, P.; Faselis, C.; Samuel, I.B.H.; et al. Cardiorespiratory Fitness and Mortality Risk Across the Spectra of Age, Race, and Sex. *J. Am. Coll. Cardiol.* **2022**, *80*, 598–609.
31. Kodama, S.; Saito, K.; Tanaka, S.; et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *JAMA* **2009**, *301*, 2024–2035.
32. Gulati, M.; Pandey, D.K.; Arnsdorf, M.F.; et al. Exercise capacity and the risk of death in women: The St James Women Take Heart Project. *Circulation* **2003**, *108*, 1554–1559.
33. Kokkinos, P.; Faselis, C.; Myers, J.; et al. Age-Specific Exercise Capacity Threshold for Mortality Risk Assessment in Male Veterans. *Circulation* **2014**, *130*, 653–658.