REVIEW

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Physical Activity and Cardiorespiratory Fitness as Modulators of Health Outcomes: A Compelling Research-Based Case Presented to the Medical Community

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Abstract

The beneficial health effects and prognostic significance of regular moderate-to-vigorous physical activity (PA), increased cardiorespiratory fitness (CRF), or both are often underappreciated by the medical community and the patients they serve. Individuals with low CRF have higher annual health care costs, higher rates of surgical complications, and are two to three times more likely to die prematurely than their fitter counterparts when matched for risk factor profile or coronary calcium score. Increased levels of habitual PA before hospitalization for acute coronary syndromes are also associated with better short-term cardiovascular outcomes. Accordingly, this review examines these relations and the potential underlying mechanisms of benefit (eg, exercise preconditioning), with specific reference to the incidence of cardiovascular, cancer, and coronavirus diseases, and the prescriptive implications and exercise thresholds for optimizing health outcomes. To assess the evidence supporting or refuting the benefits of PA and CRF, we performed a literature search (PubMed) and critically reviewed the evidence to date. In aggregate, these data are presented in the context of clarifying the impact that regular PA and/or increased CRF have on preventing and treating chronic and infectious diseases, with reference to evidence-based exercise thresholds that the medical community can embrace and promote.

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Physical inactivity (PI) represents one of the leading risk factors for global mortality.[1,2] Health organizations from across the world (eg, World Health Organization, US Department of Health and Human Services, Centers for Disease Control and Prevention, American College of Sports Medicine, American Heart Association, and the American Cancer Society) recommend that adults engage in regular moderate-intensity physical activity (PA) to help prevent, manage, and treat numerous chronic diseases including cardiovascular disease (CVD), stroke, diabetes, and cancer. However, the beneficial effects of increased lifestyle PA, structured exercise, or both remain underestimated by many clinicians and the public at large. Consequently, the health burden of PI continues to grow with technologic advances, suboptimal community landscape planning, and inadequate emphasis during clinical encounters.[3]

In this review, we highlight recent studies detailing the profound and favorable impact that regular PA and increased levels of cardiorespiratory fitness (CRF) have on health outcomes related to CVD, cancer, and coronavirus disease 2019 (COVID-19) which represent the top three leading causes of death in the United States in 2020[4] and 2021.[5] First, we discuss how PA and increased CRF impact health outcomes with specific reference to survival, decreasing CVD events, CVD and all-cause mortality, and prognostic variables such as coronary heart disease (CHD) risk factor profile, coronary artery calcium score, and health care costs. In addition, we discuss

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the role of increased PA and/or CRF before hospitalization for acute coronary syndromes (ACS) and elective or emergent short-term surgical outcomes, including the underappreciated value of exercise preconditioning as a cardioprotective phenotype. We also address the independent and additive benefits that increased PA and CRF have on commonly prescribed cardioprotective pharmacotherapies. Next, we discuss the relation of PA and CRF to cancer incidence and outcomes and COVID-19 hospitalizations and mortality. Finally, we present exercise training recommendations and evidence-based thresholds for optimizing health outcomes.

ARTICLE HIGHLIGHTS

- Physical inactivity is a global public health problem. Numerous health organizations across the world recommend engaging in physical activity (PA) to enhance health and well-being. However, the beneficial effects of increased PA and cardiorespiratory fitness (CRF) remain underappreciated by many clinicians and the public at large.
- Regular PA and increased CRF are associated with improved health outcomes, including increased survival and decreased cardiovascular disease events, chronic disease, cardiovascular disease- and all-cause mortality, and health care costs.
- Increased PA and/or CRF before hospitalization for acute coronary syndrome and elective or emergent surgery favor more positive short-term outcomes; the former activities underscore the value of exercise preconditioning as a cardioprotective phenotype.
- The effects of increased PA and/or CRF on cardioprotective pharmacotherapies and coronavirus disease 2019 hospitalizations and mortality are likely manifested as independent and additive benefits.

PA AND CRF TERMINOLOGY AND MEASUREMENT

In the context of this review, is important to distinguish between PA, exercise, and CRF. Physical activity is defined as bodily movement resulting from the contraction of skeletal muscle that increases energy expenditure above the resting level.[6] Exercise represents a subcategory of PA that is planned, structured, repetitive, and for the purpose of maintaining or improving CRF, health, athletic performance, or combinations thereof.[6] Cardiorespiratory fitness is defined as the capacity of the cardiovascular (CV) and respiratory systems to supply oxygen to the working skeletal muscles during PA.[6,7] It is also referred to as aerobic capacity or peak or maximal oxygen consumption. Importantly, PA and structured exercise are health behaviors and CRF is a health outcome of these behaviors.

Physical activity can be estimated through self-reported questionnaires or measured directly with wearable activity trackers. The duration of PA is commonly reported as minutes/week and the intensity of PA as metabolic equivalents (METs), where 1 MET (3.5 mL O_2/kg per minute) corresponds to resting energy expenditure. Accordingly, PA can be expressed using multiples of the resting energy expenditure; for example, 2 METs represents two times the resting aerobic requirement. Cardiorespiratory fitness can be directly measured during cardiopulmonary exercise testing or estimated from the attained workload, adjusted for the duration of exercise. It can also be estimated from prediction equations. Cardiorespiratory fitness is commonly expressed as mL O_2/kg per minute or METs. Previous studies have generally reported PA and CRF data that are estimated rather than measured directly. Estimated PA data, in particular, derived from self-reported questionnaires,[8] have limited reliability and validity. Similarly, errors associated with estimations of CRF also present limitations.[9] Therefore, estimated PA and CRF data along with their clinical utility should be interpreted with caution.

METHODS

To assess the evidence supporting or refuting the potential health benefits of PA and CRF, we performed an electronic

literature search using the following key words: cardiorespiratory fitness, exercise, lifestyle physical activity, physical activity, physical inactivity, and structured exercise. Specifically, we searched articles (original, review, and editorials) published in peer-reviewed journals indexed on PubMed. The literature search included articles published in English between 1950 and 2022. Because this review was focused on providing new updates, specific reference to literature published over the past decade was given.

PA AS A PROGNOSTIC INDICATOR

In 1953, Morris et al[10] reported that physically active bus conductors and mail delivery postmen had a 50% lower event rate from CHD compared with their sedentary bus driver and clerical postal worker counterparts. Because habitually sedentary individuals have an increased prevalence of 25 chronic diseases, the phrase "sedentary death syndrome" was coined to signify the emerging entity of sedentary lifestyle—mediated unhealthy conditions, almost all of which are chronic diseases or risk factors for chronic diseases that ultimately result in increased mortality.[11] In an early meta-analysis[12] of 43 studies of the relation between PA and CHD incidence, the relative risk of CHD corresponding to PI ranged from 1.5 to 2.4, with a median value of 1.9. 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[13] of 33 PA studies including 883,372 participants reported pooled risk reductions of 35% and 33% for CVD and all-cause mortality, respectively, among the most physically active cohorts. More recently, Li et al[14] estimated the influence of five low-risk lifestyle factors (never smoking, body mass index of 18.5 to 24.9 kg/m^2, $\geq$30 minutes per day of moderate-to-vigorous PA, moderate alcohol intake, and a healthy diet score) on premature mortality and life expectancy in the US population. During the follow-up period, which extended up to 34 years for some participants, the most physically active cohorts of men and women showed 7- to 8-year gains in life expectancy.

PA AND CRF AS MODULATORS OF CHRONIC DISEASE: COMPARATIVE BENEFITS

Evidence suggests that CRF is one of the strongest prognostic markers in persons

with and without chronic disease, including CHD.[15-17] In fact, two widely cited studies[18,19] that compared CRF vs PA patterns using progressive percentiles and quartiles, respectively, found that estimated CRF was a stronger predictor of mortality than self-reported PA. Interestingly, a 1000-Kcal/week increase in PA was similar to a 1-MET increase in CRF; both conferred a mortality benefit of 20%.[19] However, others contend that with self-reported PA assessments, the magnitude of associations with health outcomes are significantly underestimated, especially when compared with accelerometry measured PA.[20,21]

Over the last 2 decades, considerable evidence from large well-designed epidemiologic

studies with diverse populations supports an inverse association between CRF and the incidence of hypertension,[22-24] type 2 diabetes,[25,26] atrial fibrillation,[27] chronic kidney disease,[28] inflammation,[29,30] and major adverse CVD events,[31] including heart failure,[32-34] myocardial infarction (MI), coronary artery bypass grafting surgery, stroke, and death. These health benefits are realized at relatively moderate levels of exercise or PA and increase in a dose-response fashion, independent of other comorbidities.[35] Consequently, PI and low levels of CRF have now been designated as clinical vital signs and risk factors for CVD.[36]

CRF AND CVD- AND ALL-CAUSE MORTALITY

Blair et al[37] reported an inverse relationship between estimated CRF expressed as mL O_2/kg per minute or METs and CVD and all-cause mortality in a large cohort of middle-aged men and women (n=13,344), but noted an "asymptote of gain" beyond which further improvements in CRF conferred no additional survival benefit.

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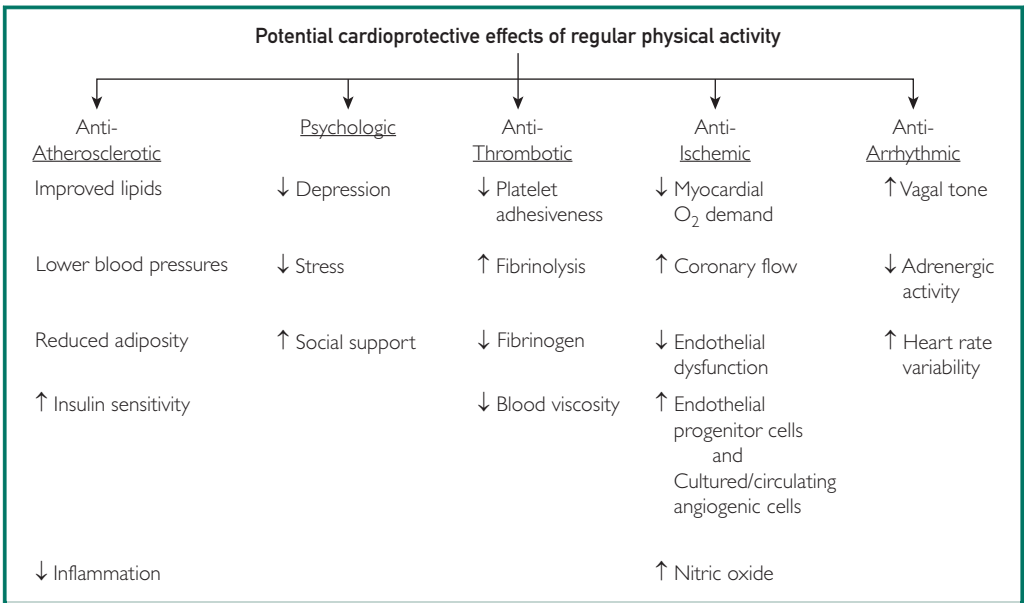

FIGURE 1. Multiple mechanisms by which moderate-to-vigorous physical activity may reduce the risk of initial and recurrent cardiovascular events; ↑ = increased, ↓ = decreased, O_2 = oxygen.

This asymptote was estimated to be ∼9 and 10 METs for women and men, respectively, approximate cutpoints that have been substantiated by others.[38-42] An exercise capacity less than 5 METs identified those with the highest mortality. Similarly, Gulati et al[38] reported that after adjusting for age and Framingham risk score, CRF was a strong independent predictor of all-cause mortality in a large cohort (n=5721) of asymptomatic women. Over an 8-year follow-up period, the Framingham risk score–adjusted mortality risk decreased by 17% for every 1-MET increase in CRF. Adjusted hazard ratios (with 95% CI) of death associated with CRF levels of less than 5, 5 to 8, and greater than 8 METs were 3.1 (2.0 to 4.7), 1.9 (1.3 to 2.9), and 1.00, respectively, highlighting the added risk associated with the least fit cohort (ie, bottom 20% [<5 METs]).

In another study of 20,950 US veterans, Kokkinos et al[31] examined the association between CRF and the risk of subsequent major CVD events. These participants had no history of previous CHD events or signs/symptoms of myocardial ischemia at the time of exercise testing. After adjusting for potential confounders, higher CRF was inversely related to the risk of CVD events. For every 1-MET increase in CRF, the risk for major CVD events was 16% lower. The adjusted risk of major CVD events across CRF categories declined progressively as exercise capacity increased. When compared with the least-fit veterans (reference group) the risk of major adverse CVD events was 68% lower for the highest fitness cohort.

Collectively, these data suggest that for the primary and secondary prevention of CHD, each 1-MET increase in CRF confers an ∼15% decrease in mortality up to 10 METs beyond which the additional survival benefits largely plateau.[39,43,44] This reduction in mortality compares favorably with the survival advantage provided by commonly prescribed cardioprotective medications (ie, low-dose aspirin, statins, β blockers, and angiotensin-converting enzyme inhibitors) after acute MI.[43] These epidemiologic analyses, when combined with investigations providing biologic plausibility (Figure 1) and other relevant reports,[45,46] support a cause-and-effect relationship between increased levels of PA and CRF and reduced CVD mortality, rather

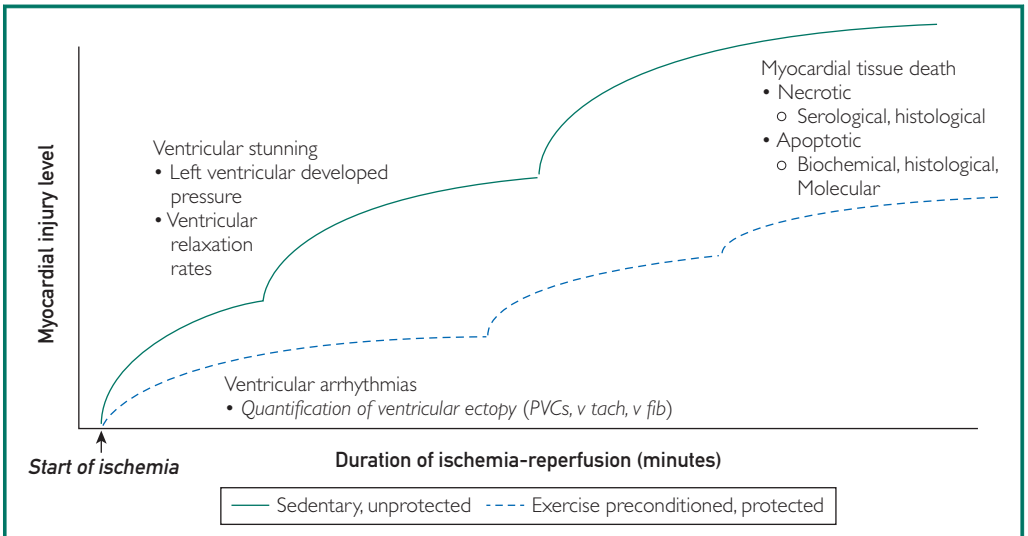

FIGURE 2. A comparison of exercise preconditioning vs sedentary hearts exposed to ischemia-reperfusion injury. Myocardial injury during an ischemic insult is proportional to the ischemic duration. Levels of injury are progressive and include electrical abnormalities, declines in ventricular pump function, and tissue death through necrotic and apoptotic mechanisms. Exercise preconditioning mitigates all forms of ischemic injury (dashed line). PVC, premature ventricular contractions; v-fib, ventricular fibrillation; v-tach, ventricular tachycardia. Adapted with permission from Quindry et al.[56]

than merely associations between these variables. Finally, individuals with low PA and/or CRF levels have increased CVD events at any given coronary artery calcium score,[47,48] and are two to three times more likely to die prematurely than their risk-factor–matched counterparts.[49,50]

CRF AND HEALTH CARE COSTS

Over the past 20 years, increasing data regarding the relations between CRF, daily energy expenditure, and health care costs have become available. Weiss et al[51] studied 881 consecutive patients (mean age, 59 years; 95% men) to examine the relationship between CRF and annual health care costs in the year following diagnostic treadmill testing. Many of the patients had greater than or equal to one coronary risk factor and others had documented CVD. In unadjusted analysis, total health care costs were incrementally lower by an average of 5.4% per MET increase in exercise capacity. The greatest decrease in health care costs went from an exercise capacity of less than 5 to 5.0 to 6.9 METs. Multivariable analysis further showed that the CRF (expressed as peak METs) achieved during exercise testing proved to be the most significant predictor of subsequent health care costs.

Similarly, Mitchell et al[52] conducted a prospective study of 6679 men (mean ± SD age, 44.8±9.1 years; 97% White) to examine the relationship between estimated CRF during maximal treadmill testing and health care costs, including physician office visits and overnight hospital stays, during the 1-year period before each of two preventive medicine exams. A subset (n=2974) was evaluated to assess whether improvements in CRF were associated with reduced health care expenditures. Men in the highest fitness quartile and those who became fit showed an ~50% reduction in direct health care costs.

More recently, Myers et al,[53] using the Veterans Exercise Testing database, reported that each 1-MET higher level of CRF was associated with $1592 annual reduction in health care costs/person, corresponding to a 5.6% lower cost per MET. Another report from George et al[54] linked lower intensities of peak daily energy expenditure, estimated

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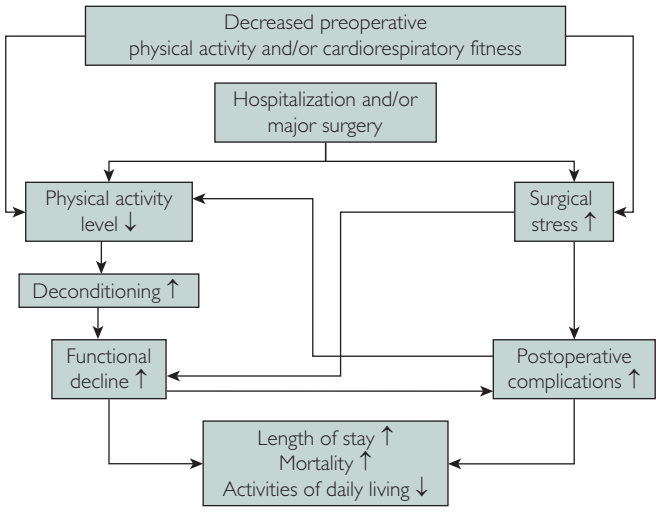

FIGURE 3. Possible impact of decreased preoperative functional status on hospitalized patients undergoing emergent or elective surgery with specific reference to outcomes. ↑ = increased, ↓ = decreased. Reprinted with permission from Hoogeboom et al.[67,69]

from the heart rate fluctuations obtained during ambulatory electrocardiographic monitoring, with increased health care use. These findings and those from Martin et al[55] suggest that increased levels of CRF as well as structured exercise or leisure-time PA interventions reduce the likelihood of using inpatient and outpatient health care services and their associated costs.

IMPACT OF CHRONIC PA ON HOSPITALIZATION FOR ACS

Increased levels of PA before hospitalization for ACS may confer more favorable short-term outcomes, likely due at least in part to exercise preconditioning.[56] An early 18-year follow-up investigation of 3263 longshoremen revealed that those with physically demanding jobs had lower CVD mortality rates due to CHD than their sedentary counterparts.[57] More recently, a clinical investigation of 2172 patients (mean ± SD age, 65.5±13 years; 76% men) hospitalized for ACS evaluated the effect of preadmission PA status on in-hospital and CVD outcomes 1 month after hospital discharge.[58] After adjusting for potential confounders, the most physically active cohort showed a 0.56-fold lower odds of in-hospital mortality and a 0.80-fold lower odds of recurrent CVD events within the first 30 days of hospital discharge.

First described decades ago in animal studies, recent clinical investigations confirm that exercise preconditions the human heart.[59] Exercise preconditioning occurs in response to short-term exercise bouts (1-3 days) that impose a hermetic stress on the heart such that cellular biochemistry is favorably altered and an ischemic-resistant phenotype is conferred, at least temporarily (Figure 2).[56] This is attributed to upregulation of biochemical mediators within the myocardium and persists for 9 days or longer after the exercise bout is completed.[46] The observed cardioprotective effect is believed to be threshold-dependent (minimum of 50% CRF or aerobic capacity) because neither long-term nor higher-intensity exercise regimens seem to further enhance the protected phenotype.[60-62] Particularly encouraging is the observation from preclinical studies that hearts are equally protected whether from women or men, young or old.[63] The latter is particularly important given that CVD incidence in humans occurs in proportion to advancing age. Thus, the cardioprotective

TABLE 1. Multiple Mechanisms by Which Vigorous-Intensity Exercise Training May Be More Effective Than Moderate-Intensity Exercise at Reducing Cardiovascular Risk[a,b]

↑	Parasympathetic tone
↑	Period of diastole and NO vasodilator function
↓	Shear stress on endothelial walls
↑	Artery compliance
↓	Plaque rupture
↓	Adverse ventricular remodeling
↓	Incidence AF and/or HF
↓	Endothelial dysfunction and myocardial ischemia
↓	Arrhythmias
↑	Heart rate variability
↓	Sympathetic outflow
↓	Inflammation

[a]AF, atrial fibrillation; HF, heart failure; NO, nitric oxide; ↑ = increased; ↓ = decreased.
[b]Adapted with permission from Franklin et al.[107]

benefits of exercise preconditioning can be rapidly evoked regardless of past/present levels of sedentary behavior or CRF and extend indefinitely for those who engage in regular moderate-intensity exercise.

IMPACT OF PA AND CRF ON SURGICAL OUTCOMES

In addition to being a strong predictor of CVD- and all-cause mortality in both asymptomatic and clinically referred populations, CRF appears to be especially helpful in the preoperative risk assessment of patients undergoing coronary artery bypass grafting,[64] abdominal aortic aneurysm repair, bariatric surgery,[65] and other surgical interventions.[36,66] Short-term complications after major surgery, including morbidity and mortality, have been linked to reduced preoperative levels of PA or CRF (Figure 3).[67] In our experience, a preoperative exercise capacity of less than 5 METs heralds the patient at increased surgical risk.[64,65] It has been suggested that patients with higher levels of CRF are simply better able to cope with the aerobic and myocardial demands created by the trauma of major surgery. Reduced aerobic capacity may also be associated with greater numbers and greater severity of unhealthy comorbid conditions that individually or collectively could increase mortality. Another proposed explanation is that a low CRF identifies a subset of patients who are more difficult to operate on, requiring longer operative and intubation times, or those characterized by a high-risk, proinflammatory state that could be related to the development of heightened postoperative complications.[65] Importantly, optimizing CRF before surgery through prehabilitation[68] is an effective strategy for enhancing physical function needed to reduce risk for adverse advents, improve postoperative recovery, and facilitate return to normal activities.

BEYOND PHARMACOTHERAPIES: INDEPENDENT AND ADDITIVE BENEFITS OF PA/CRF

A healthy lifestyle plays an important role in the primary and secondary prevention of CVD, even among those taking cardioprotective medications.[69,70] Moreover, effect estimates show convincingly that the health benefits of lifestyle changes in patients with CHD, including regular moderate-to-vigorous PA and increased CRF, are similar to or greater than those conferred by cardioprotective medications after acute MI.[69] Collectively, these findings suggest that the effects of lifestyle change in combination with drug therapy on CV risk reduction appear to be independent and additive.

To address the potential interactive effects of CRF and statin treatment on mortality risk in veterans with dyslipidemia, Kokkinos et al[71] studied more than 10,000 qualifying patients (mean ± SD, 58.8±10.9 years) over a 10-year follow-up period. Statin- and nonstatin-treated fit (CRF, 7.1 to 9 METs) and highly fit patients (CRF, >9 METs) showed a 60% to 70% reduction in all-cause mortality risk as compared with the least fit (≤5 METs). Most interesting was that highly fit patients not treated with statins had a 47% lower risk of mortality than unfit patients who were taking statins. A synergistic effect between statin therapy and CRF was also evident as patients who were taking statins and were highly fit

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TABLE 2. Minimum Work Rates ($kg \cdot m \cdot min^{-1}$) to Achieve an Energy Expenditure of ~3.5 METs on the Cycle Ergometer at Progressive Body Weights[a,b,c]

Body weight		Minimum work rate
kg	lb	($kg \cdot m \cdot min^{-1}$)
50	110	200
60	132	250
70	154	300
80	176	350
90	198	400
100	220	450
110	242	500
120	264	550
130	286	600

[a]MET, metabolic equivalent.
[b]Estimated energy expenditure of ~3.5 METs is achieved after 3 or more minutes at this work rate.
[c]Values were calculated using the energy expenditure equations developed by the American College of Sports Medicine.[113]

had the lowest mortality risk. It was concluded that "the combination of statin treatment and increased CRF resulted in substantially lower mortality risk than either alone, reinforcing the importance of PA for individuals with dyslipidemia." Another meta-analysis comparing the effectiveness of exercise therapy vs drug treatment on mortality outcomes in the secondary prevention of atherosclerotic CVD reported similar benefits.[72] Finally, it is important to emphasize that exercise training during CV rehabilitation also offers critical benefits for patients with CVD. Specifically, increased CRF through outpatient cardiovascular rehabilitation improves prognosis and major outcomes including long-term survival.[73]

PA AND CRF AS MODULATORS OF CANCER INCIDENCE AND OUTCOMES

Physical activity also plays an important role in the prevention and treatment of cancer, which is the second leading cause of death in the United States.[4,5] In a pooled analysis of 1.44 million individuals, higher levels of leisure-time PA were associated with a lower risk of 13 of 26 cancers evaluated.[74] Additionally, independent scientific review committees established by the US Department of Health and Human Services[75] and American College of Sports Medicine[76] came to similar conclusions in that there is strong evidence to support the benefits of regular PA for the prevention of seven types of cancer including breast, colon, endometrial, kidney, bladder, esophageal, and stomach. Accumulating evidence also suggests that CRF is inversely associated with the incidence of cancer.[77–80] For example, data from the Henry Ford Exercise Testing cohort[80] showed that individuals with high CRF (METs ≥12) had a 61% and 77% decreased risk of colon and lung cancer, respectively, when compared with those individuals with low CRF (<6 METs) which is consistent with other reports.[77–79] After cancer diagnosis, CRF may also impact survival. In a systematic review[81] that included 71,654 individuals and 2002 cases of cancer mortality, individuals diagnosed with cancer that had the highest CRF had a 45% reduced risk of cancer mortality compared with those with lowest CRF. Collectively, these data suggest that regular moderate-to-vigorous lifestyle PA and increased CRF are associated with reduced cancer risk and better survival outcomes among individuals diagnosed with cancer.

Cancer survivors are also at increased risk of morbidity and mortality from other chronic diseases, most notably CVD.[82,83] This increased risk of CVD may result from CV injury from cancer related therapies and concomitant lifestyle changes.[84] Recently, the American Heart Association[85] introduced the concept of cardio-oncology rehabilitation, which emphasizes that individuals treated for cancer represent a cohort at increased CVD risk who may benefit from adjunctive CV rehabilitation. A systematic review and meta-analysis[86] of six studies including 281 cancer survivors who completed CV rehabilitation showed that this intervention was associated with improvements in CRF (standardized mean difference, 0.42; 95% CI, 0.27-0.57), corresponding to an increase of 2.58 mL O_2/kg per minute for peak oxygen consumption. In related work, Stout et al[87] evaluated

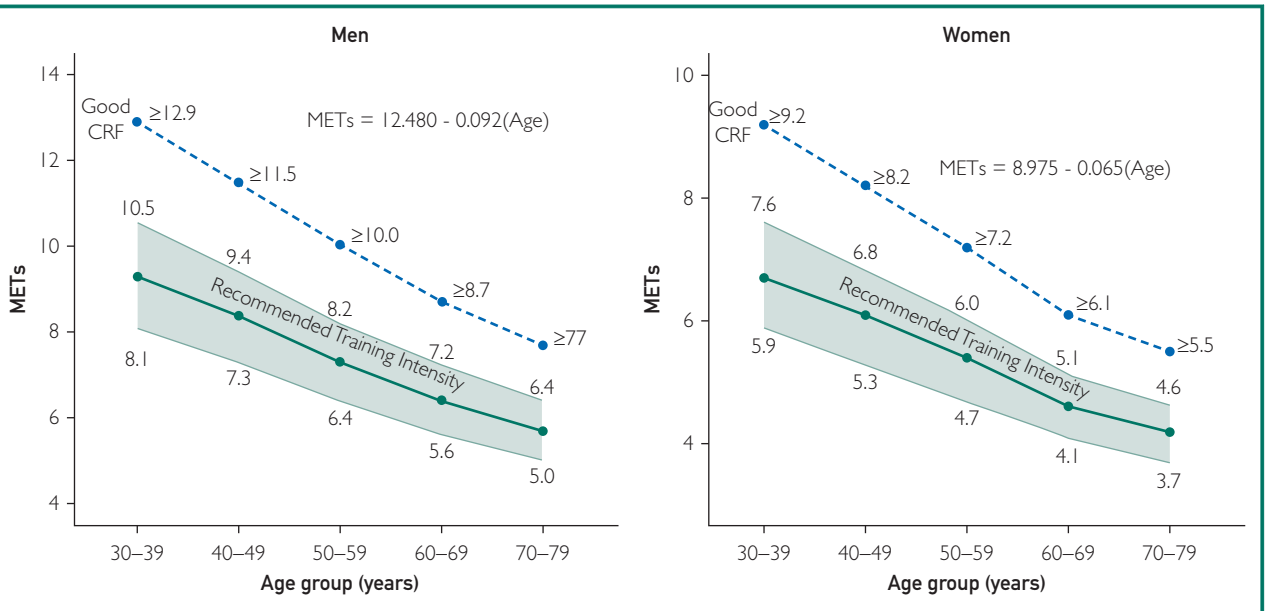

FIGURE 4. Age- and sex-adjusted "good" levels of cardiorespiratory fitness (CRF) for men and women and the recommended training intensity (60% to 80% oxygen uptake reserve [$\dot{V}O_2R$], expressed as metabolic equivalents [METs]) to achieve these fitness levels. Regression equations signify 70% $\dot{V}O_2R$. Reprinted with permission from Franklin et al.[114]

the benefits of exercise interventions for cancer survivors through an analysis of 51 relevant systematic reviews and meta-analyses. Stout et al[87] concluded that there was strong evidence for including exercise interventions as part of "every individual's cancer care plan."

PA AND CRF AS MODULATORS OF COVID-19 OUTCOMES

The lingering COVID-19 pandemic has been particularly devastating in the United States. Numerous reasons have been offered to explain the disproportionate impact on some demographic subsets (eg, Hispanic, Black, and Native Americans), including population disparities as well as the social determinants of health, for example, personal lifestyle choices.[88] Clearly, markedly abnormal risk factors and unhealthy lifestyle habits must be identified earlier and favorably modified, considering their exacerbating impact on chronic disease and COVID-19.[89]

Recently, investigators evaluated whether consistently meeting PA guidelines was associated with a reduced likelihood for hospitalization, intensive care unit (ICU) admission, and death among patients with COVID-19.[90] More than 48,000 adult patients in the Kaiser Permanente health care system were identified with a COVID-19 diagnosis between January and October 2020. All had three or more self-reported PA assessments from March 2018 to March 2020. Patients were classified into three categories: consistently inactive, 0 to 10 min/week; some activity, 11 to 149 min/week; and consistently meeting guidelines, 150+ min/week. The least active cohort had a greater risk of COVID-19 hospitalization (odds ratio [OR], 2.26; 95% CI, 1.81 to 2.83), admission to the ICU (OR, 1.73; 95% CI, 1.18 to 2.55) and death (OR, 2.49; 95% CI, 1.33 to 4.67) than patients who were consistently meeting PA guidelines. When compared with consistently inactive patients, those in the middle category (ie, some activity) also had lower odds for hospitalization, admission to the ICU, and death, suggesting that any amount of PA may be beneficial. Importantly, these findings held after adjusting for potential demographic and risk factors that may have served as

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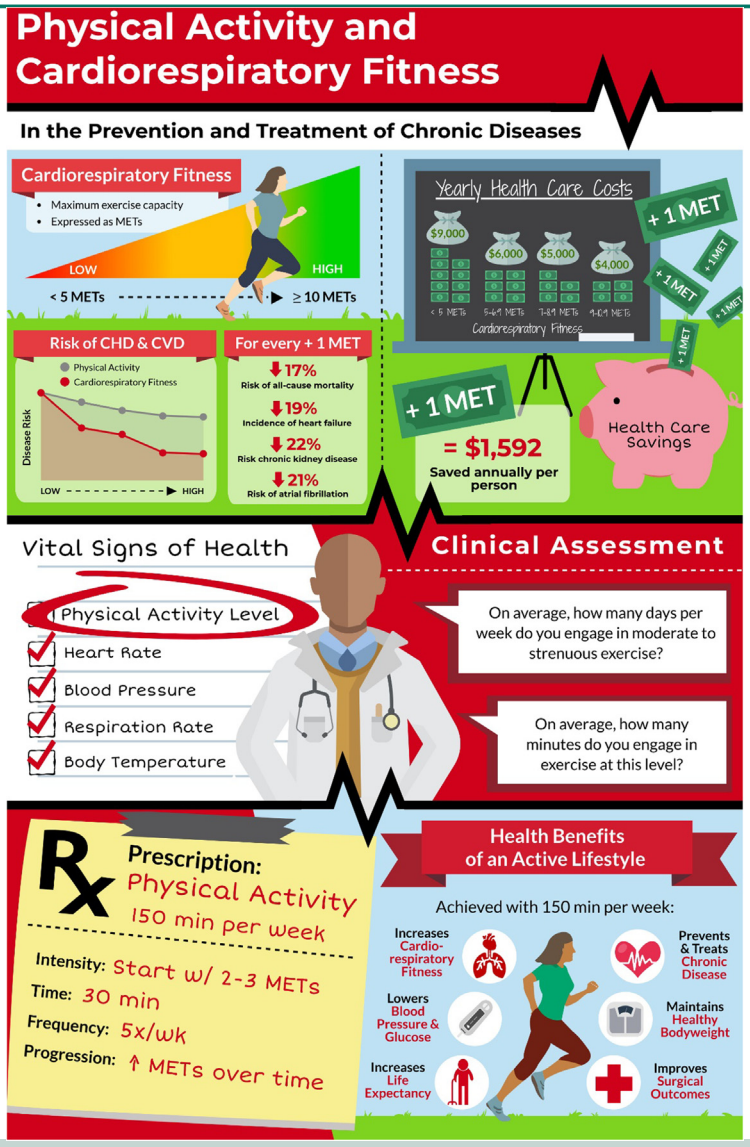

FIGURE 5. Selected improved health outcomes resulting from structured exercise programs, increased lifestyle physical activity, and/or augmented cardiorespiratory fitness and specific exercise thresholds for optimizing health outcomes. CHD, coronary heart disease; CVD, cardiovascular disease; MET, metabolic equivalent.

confounding variables. In fact, being consistently inactive was a stronger risk factor for severe COVID-19 outcomes than any of the underlying medical conditions or major modifiable risk factors except for age and a history of organ transplantation. The investigators concluded that the potential for habitual PA to lower COVID-19 illness severity should be promoted by the medical community and included in pandemic control recommendations.[90]

Another retrospective study from Brawner et al[91] evaluated the relationship between estimated exercise capacity (expressed as METs) during clinically indicated peak or symptom-limited treadmill testing performed before severe acute respiratory syndrome coronavirus 2 infection and hospitalization due to COVID-19. Logistic regression was used to adjust for potential confounders previously identified as being associated with severe illness from COVID-19. The

study population (n=246; mean ± SD, 59±12 years; 42% men; 75% Black) all underwent exercise testing and tested positive for severe acute respiratory syndrome coronavirus 2 infection; of these, 89 (36%) were hospitalized. Peak METs were significantly lower among patients who were hospitalized vs those who were not (6.7±2.8 METs and 8.0±2.4 METs, respectively). Exercise capacity was inversely related to the likelihood of hospitalization in the adjusted model, with each 1-MET increase associated with 13% lower odds for hospitalization. The investigators suggested that the inverse relationship may be attributed to the reduced risk of infection, incident chronic disease, and adverse health outcomes in aerobically fit individuals with and without underlying medical conditions, as recently summarized.[92] These results were supported by a large case control study that included 279,455 adults and confirmed that patients with more severe COVID-19 had significantly lower CRF.[93] Additionally, although obesity and central obesity have been related with increased severity of COVID-19 outcomes, several investigators[94–98] have shown that CRF appeared to be more important than weight,[99] although it was pointed out that this investigation only assessed hospitalizations, and obesity may be associated with more ICU admissions, mechanical ventilation, and deaths. These intriguing findings further support the relationship between CRF and health outcomes during the COVID-19 pandemic and beyond.[100]

EXERCISE PRESCRIPTION: MAXIMIZING HEALTH OUTCOMES

The 2020 World Health Organization Guidelines[101] on PA advise adults to engage in at least 150 to 300 minutes of moderate-intensity PA or 75 to 150 minutes of vigorous-intensity aerobic PA, or combinations thereof, throughout the week. The aerobic component should be complemented by muscle strengthening activities 2 days/week or more and limiting sedentary behaviors which have been increasingly linked to adverse health outcomes. This differs from previous guidelines as it now includes moderate-to-vigorous PA ranges rather than a minimum volume only, which acknowledges that larger PA volumes yield dose-dependent health benefits. Nevertheless, the relationship between PA volumes and CVD outcomes is perhaps best described as curvilinear, with the largest risk reductions at the beginning of the curve and eventually plateauing. Despite the dose-dependent relationship, others have reported health benefits at PA volumes below these thresholds: just 15 min/day of moderate-intensity activities (ie, brisk walking)[102] or 8-minutes/day of vigorous-intensity PA (ie, jogging or running)[103] are associated with mortality reductions of 14% and 30%, respectively. In tandem with these findings, the recent guidelines[101] deleted the previous recommendation that PA should be performed in greater than or equal to 10-minute bouts. Accordingly, over the past decade, data from wearable activity trackers has revealed the independent and additive health benefits of accumulated bouts of very brief (1-2 minutes) PA throughout the day.[20,21]

CARDIOPROTECTIVE BENEFITS OF VIGOROUS VS MODERATE-INTENSITY PA

The mortality reduction associated with a regular 5-minute run approximates a 15-minute walk and a 25-minute run is comparable to a 105-minute walk.[102] Thus, for those seeking a time-saving alternative to moderate-intensity continuous training, vigorous exercise may be preferred. Why vigorous-intensity exercise provides greater CVD benefits than moderate-intensity PA, even when the energy expenditure is equated,[104] may be due to several factors. Vigorous exercise intensities are more effective than moderate intensities at increasing CRF.[105] This understanding has additional prognostic significance because the level of CRF, expressed as mL O_2/kg per minute or as METs, is inversely related to the risk of CVD morbidity and mortality.[18] Other possible mechanisms associated with the added cardioprotective benefits of vigorous-intensity exercise training include decreased inflammation and endothelial dysfunction, increased arterial compliance and

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parasympathetic tone, and escalating reliance on carbohydrate use over fat metabolism evoked by increased adrenergic stimulation at higher exercise intensities, resulting in improvements in insulin sensitivity in obese individuals with and without diabetes mellitus.[106] Additional specific mechanisms associated with the incremental and additive cardioprotective benefits of vigorous-intensity exercise training are shown in Table 1.[107]

MINIMUM TRAINING THRESHOLDS

The minimum exercise training threshold can be expressed as steps per day, using the concept of MET-minutes per week, or as the training intensity required to vacate the least fit, least active, high-risk population cohort (ie, the bottom 20%) which corresponds to an exercise capacity of less than or equal to 5 METs. Each of these thresholds is briefly described below.

Steps Per Day

Although 10,000 steps/day has been the traditional recommendation, even fewer steps per day appear to confer survival benefits. The recent CARDIA (Coronary Artery Risk Development in Young Adults) study[108] of 2100 Black and White men and women (38-50 years of age) with a mean follow-up of 10.8 years reported that participants taking greater than or equal to 7000 steps/day, compared with fewer than 7000 steps/day, had a 50% to 70% lower risk of mortality. Accordingly, these findings suggest a viable alternative to a moderate-to-vigorous PA regimen to improve survival and life expectancy.

The MET-Minute/Week Threshold

In addition to contemporary PA recommendations, steps per day, and the personalized activity intelligence score of greater than or equal to 100 per week,[109] the research-based concept of MET-minutes per week has been validated and widely promulgated.[110] This metric enables clinicians to translate guideline-driven PA recommendations (≥500 to 1000 MET-minutes per week), based on a single formula: METs per activity × number of minutes per session × days/week. For example, 60 minutes of level walking at a 3-mph pace (∼3.4 METs), 3 days/week = 612 MET-minutes per week, which fulfills the minimum criteria (≥500 MET-minutes per week) for an effective weekly exercise dosage, yielding significant health benefits.

Minimum Exercise Training Intensity

An exercise capacity or CRF less than or equal to 5 METs is consistently associated with the poorest prognosis, corresponding to the least fit, least active population cohort (ie, bottom 20%).[19,37,38] Moreover, emerging from this fitness level appears to confer the greatest relative reduction in mortality with increasing levels of fitness (ie, progressing from ≤5 METs to >5 METs), and the most pronounced relative increase in survival.[18,19] In general, empiric experience suggests an exercise capacity greater than 5 METs can be achieved by regularly exercising above 3 METs. However, these absolute MET cut-points for exercise capacity and training intensity will vary according to age and sex.[111] An exercise intensity of 3 METs also corresponds to moderate-to-vigorous PA, which has been consistently shown to reduce the health risks associated with chronic diseases, including CVD.[112] Using the treadmill, irrespective of age, sex, weight, or fitness, this corresponds to walking at 2.0 mph, 3.5% grade, or on the level (0% grade) at 3.0 mph. Accordingly, both of these workloads equate to ∼3.4 METs. A similar MET level on the stationary cycle ergometer, adjusted for body weight, is shown in Table 2.[113]

ULTIMATE GOAL TRAINING INTENSITIES

Because the added survival benefits when progressing from "good" to "excellent" levels of CRF are very small,[37,49] ultimately achieving an age/sex adjusted "good" fitness level should be a primary exercise training

goal or objective.[114] Good fitness levels and recommended aerobic training requirements to achieve these for men and women (30-79 years of age), corresponding to 60% to 80% oxygen consumption ($\dot{V}O_2R$), are shown in Figure 4.[114] In our experience, if patients can progress to these training intensities over time without adverse signs/symptoms or excessive ratings of perceived exertion (ie, $\geq$ "hard work"), it is likely that they can attain fitness levels that are compatible with increased survival. For example, "good" fitness for a 65-year-old man approximates greater than or equal to 8.7 METs. A training intensity of 5.6 to 7.2 METs or 6.4 METs (70% $\dot{V}O_2R$), achieved over time, should enable this patient to attain "good" fitness during subsequent exercise testing. Although not all patients will achieve "good" fitness levels for age/sex, by exercising at 3 METs or greater most will be able to achieve an exercise capacity greater than 5 METs, which appears to provide the greatest relative reduction in mortality.[18,19]

EXERCISE AS MEDICINE

Regular moderate-to-vigorous intensity exercise has been described as "a miracle drug that can benefit every part of the body and substantially extend lifespan."[115] Unfortunately, many clinicians do not emphasize the salutary impact of regular PA and/or increased CRF, as well as the harms of PI, even though they routinely counsel patients about modifiable CVD risk factors. As a resource for clinicians, Figure 5 highlights many of the improved health outcomes resulting from structured exercise programs, increased levels of lifestyle PA and/or CRF, and specific exercise thresholds. Finally, common characteristics of the world's longest living populations (eg, Sardinians, Adventists, and Okinawans) include daily PA[116]; thus, a prescription to walk 30 minutes per day could be one of the most important recommendations a patient could receive.[117]

HEALTH CARE DISPARITIES AND FITNESS

As recently reviewed,[118] the African-American (AA) population has higher prevalence of obesity, lower levels of CRF, and worse COVID-19 outcomes than do White individuals. Additionally, the AA population may even have a lower response to improve CRF following formal exercise training programs.[16-19] Considering the recent attention[19,119] directed at health disparities in many areas, including COVID-19, greater efforts are needed to reduce obesity and improve levels of PA and CRF, possibly with higher intensity exercise training, to improve CRF and subsequent health outcomes in the AA population, including in future pandemics.

CONCLUSION

This review describes how regular PA and increased CRF have a profound impact on preventing and treating chronic and infectious disease. The data presented herein also provide comprehensive and evidence-based exercise thresholds for a treatment effect. Moving forward, it is imperative that clinicians, public health officials, and fitness professionals work together to promote PA and improved CRF for individuals and their communities.

POTENTIAL COMPETING INTERESTS

The authors report no potential competing interests.

Abbreviations and Acronyms: **AA,** African American; **ACS,** acute coronary syndrome; **CHD,** coronary heart disease; **COVID-19,** coronavirus disease 2019; **CRF,** cardiorespiratory fitness; **CV,** cardiovascular; **CVD,** cardiovascular disease; **MET,** metabolic equivalent; **PA,** physical activity; **PI,** physical inactivity

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