Sedentary Behavior, Exercise, and Cardiovascular Health

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Abstract: **Sedentary behavior and physical inactivity are among the leading modifiable risk factors worldwide for cardiovascular disease and all-cause mortality. The promotion of physical activity and exercise training (ET) leading to improved levels of cardiorespiratory fitness is needed in all age groups, race, and ethnicities and both sexes to prevent many chronic diseases, especially cardiovascular disease. In this state-of-the-art review, we discuss the negative impact of sedentary behavior and physical inactivity, as well as the beneficial effects of physical activity /ET and cardiorespiratory fitness for the prevention of chronic noncommunicable diseases, including cardiovascular disease. We review the prognostic utility of cardiorespiratory fitness compared with obesity and the metabolic syndrome, as well as the increase of physical activity /ET for patients with heart failure as a therapeutic strategy, and ET dosing. Greater efforts at preventing sedentary behavior and physical inactivity while promoting physical activity, ET, and cardiorespiratory fitness are needed throughout the healthcare system worldwide and particularly in the United States in which the burden of cardiometabolic diseases remains extremely high. (*Circ Res*. 2019;124:799-815. DOI: 10.1161/CIRCRESAHA.118.312669.)**

Key Words: cardiorespiratory fitness ■ cardiovascular disease ■ exercise ■ heart failure ■ sedentary behavior

Although the American Heart Association, the American College of Cardiology, and the American College of Sports Medicine, among other leading organizations, have emphasized that sedentary behavior (SB) and physical inactivity (PI) are major modifiable cardiovascular disease (CVD) risk factors, a sizable percentage of the United States and worldwide population still present with high levels of SB/PI and low levels of physical activity (PA).[1–3] Recently, a major emphasis has been directed at making health promotion a priority, including the promotion of PA and exercise training (ET) and improving levels of cardiorespiratory fitness (CRF) in the United States and worldwide in efforts to prevent chronic diseases, especially CVD.[2,4]

In this article, we review the adverse consequences of SB and PI and the potential benefits of PA/ET on cardiovascular health. We also review the importance of CRF as perhaps one of the most important CVD risk factors, as well as the prognostic utility of fitness compared with obesity and the metabolic syndrome. The potential for ET and improvements in CRF for patients with heart failure (HF) are also reviewed, including the importance of muscular fitness in addition to aerobic fitness. Finally, we conclude by recommending areas in which greater investigative attention is needed.

SB and CVD

In addition to the positive cardiovascular health effects associated with increases in moderate and vigorous PA, there is emerging evidence of several negative health consequences associated with SB, which has been defined as any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents of task (METs), while in a seated, reclined or lying posture.[5] It is important to emphasize that SB is distinct from PI, where an individual does not perform moderate-to-vigorous PA. Although SB and PA are at opposite ends of the energy expenditure continuum,[6] the addition of a postural component as a requirement to be considered sedentary suggests that it is a unique behavior that can be intervened on. One can envision the situation where someone is physically active for the recommended 150 to 300 minutes per week,[7] yet they may sit for several hours a day in a sedentary occupation or during their leisure time.

The American Heart Association recently released a Science Advisory that highlighted the deleterious association between SB and CVD morbidity and mortality.[8] However, the American Heart Association report stopped short of making specific quantitative recommendations about target levels of SB and reinforced the need for further research that would inform future quantitative public health guidelines, including the need for interventions using randomized controlled trial designs.[8] The American Diabetes Association has incorporated SB into their recent Position Statement on PA/ET and diabetes mellitus, recommending that adults should reduce their overall SB and interrupt prolonged bouts of SB with episodes of light-intensity PA.[9] Some countries, such as

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Nonstandard Abbreviations and Acronyms

BMI	body mass index
CHD	coronary heart disease
CRF	cardiorespiratory fitness
CVD	cardiovascular disease
ET	exercise training
HDL	high-density lipoprotein
HF	heart failure
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazards ratio
LM	lean mass
LV	left ventricle
METs	metabolic equivalents of task
PA	physical activity
PGC-1α	proliferator-activated receptor γ coactivator 1-α
PI	physical inactivity
SB	sedentary behavior
SIRT	sirtuin
T2DM	type 2 diabetes mellitus
VO_2	oxygen consumption

Australia and the United Kingdom, have also begun to release SB guidelines alongside their PA guidelines,[10,11] but they do not make specific quantitative recommendations for adults. Rather, they recommend minimizing time spent sitting and breaking up periods of prolonged sitting. Given the differences in sedentary time between self-reported and objectively measured estimates and the lack of a clear threshold of SB that reduces health risks, it is difficult at the present time to provide a quantitative recommendation. Therefore, future studies are needed to use devices that objectively quantify SB to make strides towards identifying critical thresholds associated with increased risk of CVD.

The health consequences associated with SB were investigated in a series of preclinical studies conducted in the early 2000s.[12,13] Using hindlimb suspension (unloading) in a rat model to mimic human SB, a decrease in lipoprotein lipase activity (the enzyme responsible for hydrolysis of triglyceride-rich lipoproteins), triglyceride uptake into red skeletal muscle, and HDL (high-density lipoprotein) cholesterol concentration occurred within a day's time.[14] Further, a global gene-expression profiling study in rats identified 38 genes that were upregulated by SB (hindlimb unloading) and that 27 of these upregulated genes remained above control levels even after the rats returned to standing and ambulation for 4 hours.[15] Furthermore, it is well-accepted that elevated levels of oxidative stress results in pervasive systemic impairments. Mitochondrial dysfunction has been recognized as a significant source of oxidative stress. Within the skeletal muscle cells, PGC-1α (proliferator-activated receptor γ coactivator 1-α), a key regulator of mitochondrial mass/function, and NAD-dependent deacetylase SIRT3 (sirtuin-3), which promotes the expression of PGC-1α, have been found to be lower in sedentary individuals.[16] Their inverse relation with levels of reactive oxygen species may partly explain damage and mutations to DNA, which contributes to impaired mitochondrial and subsequently skeletal muscle quality and function. Experimental studies that mimicked SB in a laboratory setting have also provided evidence of greater postprandial glucose and insulin levels during bouts of prolonged sitting (ie, 7 hours) compared with individuals taking frequent standing or walking breaks.[17] Compared with prolonged sitting, breaking up sitting time with intermittent, light-intensity activity can increase expression of anti-inflammatory and antioxidative pathway modulators such as nicotinamide N-methyltransferase as well as regulators of glucose transporter type 4 translocation.[18] Individuals that chronically sit for long periods of time without intermittent activity likely have reduced expression of key metabolic regulators. Taken together, these results indicate that the gross metabolic disturbances observed with SB result from metabolic alterations at the level of the muscle. While these studies suggest some potential mechanisms involved in SB, substantially more research is required to determine the pathophysiological pathways through which SB impacts risk for CVD, and whether these pathways differ from those associated with PI.

The preclinical work described above was followed by a large number of epidemiological investigations of the associations between SB, such as daily sitting time or television viewing, and several health outcomes. The evidence is strongest for the associations between SB and mortality from CVD and all-causes and weaker for mortality from cancer.[19] However, the weaker association between SB and cancer may be explained by the fact that cancer is a highly heterogeneous disease with several different causes and related treatments. For such reasons epidemiological studies investigating the relationship between SB and cancer mortality should be interpreted with caution.

The first studies to comprehensively address the association between SB and mortality reported robust and consistent results. A study of 17 013 Canadian adults followed for an average of 12 years, reported a significant dose-response association between daily sitting time and both all-cause and CVD mortality.[20] Compared with people who reported sitting almost none of the time, those that reported sitting almost all of the time had a 54% higher risk of dying from all-causes or CVD.[20] These results were followed closely by a study that investigated the relationship between television viewing and mortality among 8800 Australian adults followed for a median of 6.6 years.[21] When compared with those who reported watching television <2 hours per day, individuals watching ≥4 hours per day experienced a 45% and 80% increased risk of all-cause and CVD mortality, respectively. The results of these early studies have been widely replicated and included in recent meta-analyses investigating the association of SB with television viewing[22] and sitting.[23] Chau et al[23] reported summary hazard ratios (HR) of 1.00 (95% CI, 0.98–1.03), 1.02 (95% CI, 0.99–1.05), and 1.05 (95% CI, 1.02–1.08) for every 1-hour increase in sitting between 0 and 3, >3 to 7, and >7 hours of daily sitting, respectively. Similarly, Sun et al[22] reported that television viewing was associated with a significant increased risk for all-cause mortality risk in a curvilinear,

direct fashion that increased steadily and more rapidly as television viewing time increased.

A recent meta-analysis investigated the association between SB and incident CVD events using data from 9 prospective cohort studies including 720 425 participants.[24] The authors reported a summary HR of 1.14 (95% CI, 1.09–1.19) comparing the highest (12.5 h/d) versus lowest levels (2.5 h/d) sedentary time. They also observed a significant increased risk at >10 h/d of sedentary time (HR=1.08; 95% CI, 1.00–1.14).[24] The reported HR of this meta-analysis seems to confirm the increased CVD risk associated with SB, however, the effects of SB may be less pronounced than what was suggested in prior smaller studies.

Interactions Between SB and PA

The effects of SB and PA on health outcomes are currently object of intense scrutiny. Several studies have reported that the relative risks associated with sedentary time are higher among people who are not regularly physically active. For example, a meta-analysis of epidemiological studies reported a summary HR associated with SB of 1.46 (95% CI, 1.22–1.75) in those with low levels of PA versus a summary HR of 1.16 (95% CI, 0.84–1.59) in those with high levels of PA.[25] In the largest study to date, Ekelund et al[26] pooled data on 1 005 791 participants to examine the combined effects of SB and PA on mortality from CVD, cancer, and all-causes, and they demonstrated that moderate-to-vigorous PA was inversely associated with CVD mortality at every level of sitting (<2, 2–5.9, 6–8, and >8 hours per day). Conversely, sitting time was associated with increased mortality. When studying the effects of SB across different PA levels, while the associations between SB and mortality was significant in individuals with lowest levels of moderate volume PA, the relationship between SB and mortality was no longer significant in individuals who were participating in ≥35.5 MET-hour per week of PA (≈60–75 minutes per day of moderate intensity PA; Figure 1).[26] Finally, the results for the joint association of television viewing and PA on CVD mortality were similar to those for sitting and PA.

In summary, in addition to the beneficial effects of PA on risk for CVD (discussed below), there is emerging evidence that excessive SB is also an important CVD risk factor, particularly in those with lowest levels of moderate volume PA. To the contrary, high levels of PA appear to attenuate the negative cardiovascular consequences of SB, but more research is required to better determine the interactions between PA/SB on health outcomes.

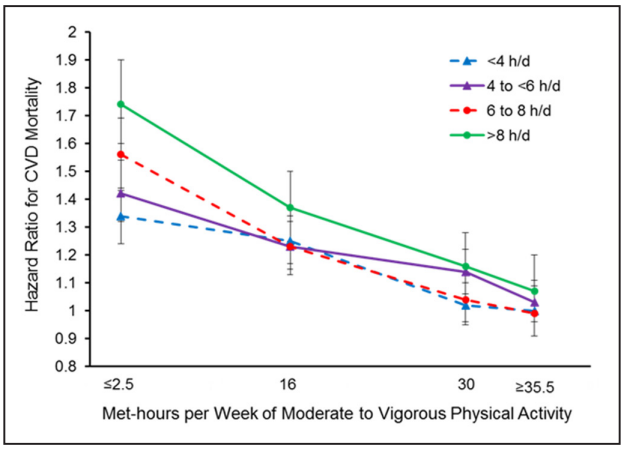

Figure 1. Hazard ratios for the joint association of sitting time and physical activity with cardiovascular disease (CVD) mortality. Data derived from appendix of Ekelund et al.[26]

Consequences of PI on Cardiovascular Health

Cardiovascular health is independently associated with PA, with PI linked with the greatest risk of developing CVD.[27,28] The prevalence of PI has increased over recent years, perhaps as the result of a greater adoption of the Western lifestyle, characterized by greater sedentary time, lower participation in active transport, and time spent in leisure or purposeful PA.[29–31] Of note, a global examination of PI and noncommunicable disease prevalence estimated that 6% of coronary artery disease, 7% of type 2 diabetes mellitus (T2DM), 10% of breast cancer, and 10% of colon cancer cases were caused by PI. Premature mortality as a result of PI accounted for over 5.3 million global deaths in 2008,[28] and in the United States, all-cause and CVD-specific mortality advanced mortality by 4 and 2.4 years, respectively.[32] By eliminating PI, it is estimated that life expectancy of the world's population would increase by 0.68 years.[28]

PI is also closely associated with metabolic disorders, such as impaired glucose metabolism, which substantially increases risk of CVD.[33] Troubling trends of an increased prevalence of T2DM in children and young adults are in part because of unhealthy lifestyle which promotes PI and the consumption of foods with low nutritional value.[34] In a longitudinal examination, 3596 Finnish youth (baseline age, 3–18 years) were followed for 31 years to determine the effects of persistent PI on glucose metabolism in adulthood.[35] Compared with participants who were persistently physically inactive, those who increased PA (relative risk, 0.47; 95% CI, 0.29–0.76) or remained persistently active had a lower relative risk for having impaired glucose metabolism at follow-up (0.70; 95% CI, 0.51–0.97). However, individuals who had decreased PA were at similar risk (relative risk, 0.93; 95% CI, 0.66–1.36) to those with persistent PI.

Although the relation between PI and cardiovascular health is independent and robust, the modulatory effects of PI on cardiovascular health are complex and not completely elucidated. Strong predictors of CVD, such as conduit arterial stiffness and reduced endothelium-dependent dilation (ie, flow-mediated dilation), have been well documented in physically inactive men and women.[36] Much of our current understanding of the vascular consequences of becoming inactive has been through extreme models of PI, such as bed rest or limb immobilization.[37–39] In contrast, Boyle et al[40] sought to implement a real-world model of PI by reducing daily PA levels of highly active volunteers (>10 000 steps per day) to PI levels (<5000 steps per day) over a 5 day period. This short exposure to a physically inactive lifestyle induced a decrease in popliteal artery flow-mediated dilation (baseline, 4.7±0.98%; day 5, 1.72±0.68%, $P<0.05$) and endothelial cell activation ($CD62E^+$), and an increase of markers of endothelial cell apoptosis ($CD31^+/CD42b^-$). In line with these findings, both preclinical and clinical investigations have identified oxidative stress as a prominent mediator of endothelial dysfunction.[41–44]

Imbalances between the production and destruction of reactive oxygen species by antioxidant defense systems associated with inactivity, promote the uncoupling of endothelial nitric oxide synthase. Such abnormalities result in reduced nitric oxide bioavailability and increased production of superoxide.[45] Prolonged disruption of endothelial function and associated reduction in vascular compliance because of PI are particularly damaging to cardiovascular health, finally imposing elevated loads on the left ventricle (LV), which may lead to LV stiffening, chamber remodeling and increasing risk of developing HF.[46,47]

PA and its Relation to Cardiovascular Health

The cardioprotective effects of regular PA, whether performed in low or high volumes, are clear and extend across all ages, sex, and race (Table 1).[27,48–61] However, much of the seminal epidemiological work quantifying the volume of PA necessary to curb health risks resulted from subjective assessments of PA, including the use of questionnaires or interviews.[62–64] Technological advancements have improved the accuracy and reliability of device-measured PA levels and have become readily available to be applied in large scale epidemiological investigations for objective assessment of PA.[65] These advancements coupled with large scale randomized controlled trials have allowed to accurately identifying the specific PA volumes associated with improved markers of cardiovascular health.[66–69] These results have made it possible to develop individualized PA recommendations, thus moving away from a one size fits all approach.[66]

Despite the known benefits of PA, the adoption of a physically active lifestyle has remained low because of various reasons: personal barriers associated with perceived limitations in self-efficacy, lack of time, and misconceptions of the volume of exercise necessary for cardiovascular health benefits. Despite the evidence supporting the cardiovascular benefits of moderate-to-vigorous PA performed even in bouts of at least 10 minutes, the level of adherence of the general population to the guidelines remains unacceptably low. A recent prospective cohort study assessing PA levels in 1274 older men, over a median follow-up of 5 years investigated the effects of bouts of PA of at least 10 minutes on mortality.[70] Accelerometers were used to quantify moderate-to-vigorous PA accumulated in sporadic minutes of PA or in bouts lasting ≥10 minutes. Over the course of a 7-day PA assessment period, only 16% of the older men met the recommended volume of PA when applying the ≥10 minutes criteria, whereas 66% of older men achieved 150 minutes of recommended activity with minutes of accumulated sporadic PA. Despite these stark differences in the proportion meeting PA recommendations, HR for all-cause mortality when PA was accumulated sporadically (HR, 0.59 [95% CI, 0.43–0.81]) did not differ from when PA was performed in ≥10 minutes bouts (HR, 0.58 [95% CI, 0.33–1.00]), suggesting that participation in PA is beneficial irrespective of how it is accumulated. However, this study only included older men, clearly requiring further validation in younger populations and in women, finally allowing to potentially develop even more individualized PA recommendations.

The benefits of PA on cardiovascular health and to combat the aging process are multifaceted (Figure 2).[71–97] Aging is associated with a decline in LV as well as vascular function, finally altering the interaction between the LV and arterial system (ventricular-arterial coupling). The impairment in ventricular-arterial coupling is related, at least in part, to an increase in arterial stiffening, which increases the afterload on the heart and consequently increases LV stiffening. Prolonged exposure to these conditions as it occurs with aging increases the risk of developing HF. However, lifelong exercise, 4 to 5 sessions per week can prevent age-related decrements in compliance and distensibility,[68] while maintaining youthful arterial compliance and function.[69] Although the exact mechanisms responsible for the above described ET-induced cardiovascular benefits are not clear, several hypotheses have been proposed. Rodent models have provided evidence that ET enhances calcium handling through the sarcoendoplasmic reticulum calcium transport ATPase as well as an increase in its mRNA expression.[70,98] Furthermore, ET reduces circulating markers of systemic inflammation, such as C-reactive protein,[99] which may protect against inflammation-mediated myocardial fibrosis and dysfunction. In regard to the peripheral vasculature, regular PA can reduce mitochondrial reactive oxygen species production, enhance cellular antioxidant defense proteins, and reduce mitochondrial fission (a sign of mitochondrial dysfunction).[100] Collectively, these beneficial effects of ET may contribute to improving compliance, reducing stiffness, and afterload, finally reducing the risk of future cardiac dysfunction.

Importance of Cardiorespiratory Fitness

PA and ET are associated with improvements in cardiovascular health and longevity, however, much of these benefits may result from the improvements in CRF following increased PA, which is a stronger predictor of prognosis compared with PA/ET alone.[1–3,101,102] While the explanatory factors for the different prognostic ability of CRF versus PA/ET are complex, a potential reason may be related to the well-documented observations of interindividual fitness changes to the same volume of PA/ET.[103,104] The gold standard for CRF remains the measurement of peak oxygen consumption (VO_2) by cardiopulmonary exercise testing using gas exchange analysis. Other assessments of exercise capacity, such as estimated METs, determined by speed and incline on the treadmill using standard algorithms, or even 6-minute walk test, particularly in patients with coronary heart disease (CHD) and HF, have been potent predictors of prognosis.[105–108] The potential benefits of improved PA, ET, and CRF are numerous and are summarized in Table 2.

Similar to high levels of PA, high levels of CRF are associated with reduced prevalence of many CVD and CHD risk factors, including hypertension, obesity, metabolic syndrome, and T2DM.[101,102,130,131] Clearly, many studies have demonstrated the powerful impact of CRF on prognosis, which has been noted in large population-based studies, clinical cohorts, and in those at high CVD risk and in CVD populations, such as CHD and HF.[1–3,101,102,131]

Nearly a decade ago, a very high-profile meta-analysis by Kodama et al[132] of 33 studies in over 100 000 individuals observed that every 1 estimated MET increase in CRF was associated with 13% and 15% reductions in all-cause and CVD/

Table 1. Physical Activity and Prevention of CVD and CVD Related Events

Author	Population	PA Measurement	Results
Lee et al[27]	40 801 men; 14 336 women	PA questionnaire is assessing duration, distance, frequency, and speed of running or jogging.	Compared with nonrunners, runners had 30% and 45% lower adjusted risks of all-cause and CV mortality, respectively, with a 3-year life expectancy benefit. During an average 15-year follow-up, persistent runners had a 29% and 50% lower risks of all-cause and CV mortality, respectively, compared with never runners.
Florido et al[48]	4881 men; 6470 women	Baecke questionnaire	Participants maintaining PA recommendations compared with those maintaining poor activity had lower heart failure risk (0.69, 95% CI, 0.60–0.80). Individuals increasing from poor to meeting PA recommendations had reduced heart failure risk (0.77, 95% CI, 0.63–93).
O'Donovan et al[49]	27 732 men; 31 273 women	Interview is inquiring about housework, walking, sport, and exercise PA performed in previous 4 wk.	Risk of CVD mortality in overweight (1.41, 95% CI, 0.94–2.10) and obese (1.41, 95% CI, 0.84–2.38) individuals did not differ compared with normal weight individuals meeting PA guidelines.
Nes et al[50]	19 269 men; 20 029 women	PAI score	Men and women with a PAI score of ≥100 had 17% (95% CI, 7%–27%) and 23% (95% CI, 4%–38%) reduced risk of CVD mortality, respectively, compared with inactive individuals.
El Saadany et al[51]	7146 men; 8161 women	PA interview	Irregular (≤4 days/wk) PA and regular (>4 d/wk) PA were associated with lower risk of CVD mortality (0.66, 95% CI, 0.51–0.85 and 0.58, 95% CI, 0.47–0.72, respectively) compared with no activity. These observations only remained true for women and not men for irregular and regular activity.
Kubota et al[52]	34 874 men; 40 038 women	Self-administered PA questionnaire regarding leisure-time, commuting, housework PA.	Compared with the lowest quartile of daily PA, higher PA levels were associated with reduced risks of total and ischemic stroke. Highest PA level was not associated with reduced risks of hemorrhagic strokes. Second and third quartile had lowest risk of total stroke (0.83, 95% CI, 0.75–0.93 and 0.83, 95% CI, 0.75–0.92, respectively).
Lear et al[53]	54 621 men; 76 222 women	International Physical Activity Questionnaire	Individuals with moderate or high PA levels had a lower risk of major CVD (0.86, 95% CI, 0.78–0.93 and 0.75, 95% CI, 0.69–0.82, respectively) compared with those with low levels of PA.
Fishman et al[54]	1412 men; 1617 women	Accelerometer	Compared with the lowest tertile of activity, those in the second and third highest tertile had significantly lower risk of mortality (0.21, 95% CI, 0.12–0.38 and 0.36, 95% CI, 0.30–0.44, respectively).
Soares-Miranda et al[55]	1641 men; 2566 women	Minnesota Leisure-Time Activities Questionnaire	Walking pace, distance, leisure-time PA, and exercise intensity were associated with lower risk of CHD, stroke, and CVD. Highest leisure-time PA (kcal/wk) compared with lowest quintile had lower risk for CHD (0.57, 95% CI, 0.45–73), stroke (0.56, 95% CI, 0.42–0.75), and CVD (0.59, 95% CI, 0.48–0.72).
Bell et al[56]	3707 blacks; 10 018 whites	Baecke Questionnaire	PA was inversely related to CVD, heart failure, and CHD incidence in both races, and stroke in blacks.
Shortreed et al[57]	4729 men and women	Self-reported PA	Compared with long-term physical inactivity, long-term PA was associated with a CVD rate ratio of 0.95 (95% CI, 0.84–1.07), all-cause mortality rate ratio of 0.81 (95% CI, 0.71–0.93), and CVD attributable mortality rate ratio of 0.83 (95% CI, 0.72–0.97). A greater protective effect of long-term PA on CVD incidence was present for men but not women.
Gulsvik et al[58]	5653 men and women	Self-reported PA	Individuals with a high level of PA compared with low PA levels had lower all-cause (0.63, 95% CI, 0.56–0.71), ischemic heart disease (0.66, 95% CI, 0.52–0.83), and stroke (0.66, 95% CI, 0.47–0.93) mortality risk compared with no activity.
Wen et al[59]	199 265 men; 216 910 women	Leisure-time PA questionnaire	Compared with inactive individuals low-volume activity reduced all-cause mortality and extended life expectancy by 3 y. Exercise 15 min/day =14% reduced risk of all-cause mortality. Every additional 15 min of daily exercise further reduced all-cause mortality by 4% (95% CI, 2.5–7.0). Inactive individuals had a 17% (95% CI, 1.10–1.24) increased risk of mortality compared with low-volume group.

(*Continued*)

Table 1. Continued

Author	Population	PA Measurement	Results
Tjønna et al[60]	26 005 men; 27 537 women	Self-reported PA	Physically active individuals with CVD risk factors had a lower risk (HR, 0.76; 95% CI, 0.61–0.95) compared with the inactive group with CVD risk factors.
Wisløff et al[61]	27 143 men; 28 929 women	Self-reported PA	Compared with those reporting no activity, a single weekly bout of high-intensity exercise lowered risk of CVD death in men (0.61, 95% CI, 0.49–0.75) and women (0.49, 0.27–0.89). No additional benefits when increasing duration or number of sessions per week. Risk reduction increased with increasing age in men but not in women.

CHD indicates coronary heart disease; CVD, cardiovascular disease; HR, hazards ratio; PA, physical activity; and PAI, physical activity intelligence.

CHD mortality, respectively. This large meta-analysis also defined age- and sex-specific levels of CRF that were associated with lowest event rates in women (40 years: 7 METs; 50 years: 6 METs; and 60 years: 5METs) and men (40 years: 9 METs; 50 years: 8 METs; and 60 years: 7 METs).

Additionally, CRF is associated with prognosis in those individuals with high-risks of CVD, including those with metabolic syndrome, pre-T2DM or T2DM.[1–3,101,102,131,133] In such high-risk individuals, often those with high levels of CRF have a better prognosis that do unfit individuals without these disorders. High levels of CRF have also been protective against lifetime CVD risks. In fact, subjects with a high burden of CHD risk factors but increased level of CRF have lifetime CVD risks similar to or even lower than those with lower risks factors,[134] further supporting the powerful role of CRF even in those with otherwise high CVD risk.

Many studies have also investigated the effects of the changes in CRF over time on CVD risk factors and on CVD morbidity and mortality.[1–3,101,102,131,133] Particularly, Sui et al[131] have recently reviewed the impact of changes in CRF on improvements in various CVD and CHD risk factors. Using the Aerobics Center Longitudinal Study (N=9777), Blair et al[135] reported that men classified in the lowest 20th percentile of CRF based on age at their first examination but fit at the time of their second examination several years later had a 52% reduction in CVD mortality compared with men who remained unfit. Similarly, Lee et al[136] evaluated the effects of the changes in CRF on CVD mortality over a mean 11.4 years follow-up in 14 345 subjects using the same Aerobics Center Longitudinal Study data set. They demonstrated that those individuals who presented with a preserved CRF or an increased CRF after 6.3 years from the initial CRF assessment had significant reductions in CVD mortality by 27% and 42%, respectively. Importantly, for every 1 estimated MET increase, all-cause and CVD mortality were reduced by 15% and 19%, respectively. Erikssen et al[137] and others have noted similar findings about improvements in CRF over time.

The assessment of CRF represents the synergistic functioning of multiple organ systems to effectively transport oxygen from the air to the mitochondria of the working skeletal

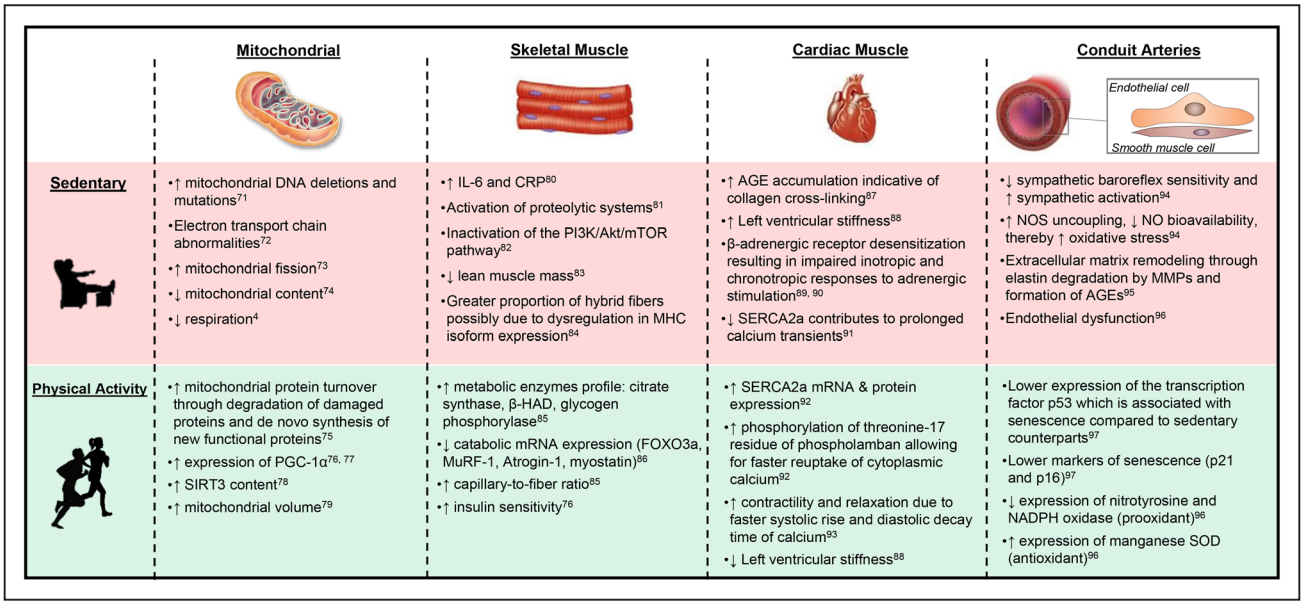

Figure 2. The multidimensional mechanisms associated with the deleterious effects of sedentary behavior and the beneficial effects of physical activity that occur within the mitochondria, skeletal muscle, myocardium, and conduit arteries. β-HAD indicates β-hydroxyacyl CoA dehydrogenase; AGE, advanced glycation end products; Akt, protein kinase B; CRP, C-reactive protein; FOXO3a, forkhead box O3;IL-6, interleukin-6; MHC, myosin heavy chain; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; MuRF-1, muscle RING-finger protein-1; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; PI3K, phosphoinositide 3-kinase; SERCA2a, sarcoplasmic reticulum calcium adenosine triphosphatase; and SIRT3; nicotinamide adenine dinucleotide-dependent deacetylase sirtuin-3 SOD.

Table 2. Potential Benefits of Physical Activity, Exercise Training, and Cardiorespiratory Fitness on Prognosis

Physiological Benefits	
Reduced blood pressure[109]	Reduced systemic inflammation[110]
Improved heart rate variability[111]	Decreased myocardial oxygen demands[112]
Improved endothelial function[113]	Maintain lean mass[114]
Improved insulin sensitivity[115]	Reduced visceral adiposity[116]
Reduced myocardial infarction[117]	Increased capillary density[118]
Reduced blood and plasma viscosity[119]	Improved mood and psychological stress[120]
Increased mitochondrial density[79]	Improved sleep[121]
Reduced risk of developing	
Hypertension[122]	Osteoporosis[123]
Depression[124]	Osteoarthritis[125]
Metabolic syndrome[126]	Dementia and Alzheimer Disease[127]
Diabetes mellitus[128]	Breast, colon, and other cancers[129]

muscle, which must produce the necessary energy to meet the demands of activity as well as effectively remove the resultant metabolic byproducts that impair the ability of the muscle to sustain activity when accumulated in excess. Considering the highly prognostic nature of CRF and its representation of the whole-body physiological function, its assessment has been used as the primary end point also in non-ET interventions (ie, pharmacological) in HF patients. Pharmacological interventions, such as angiotensin-converting enzyme inhibitors and sildenafil therapy in patients with HF with reduced ejection fraction (HFrEF) have been effective in significantly increasing CRF.[138,139] Conversely, these pharmacological interventions have not been as effective in patients with HF with preserved ejection fraction (HFpEF), highlighting the need to develop nonpharmacological therapeutics, as also described in the next paragraphs. For example, HFpEF patients randomized to 24 weeks of phosphodiesterase-5 inhibitor did not experience significant increases in CRF or clinical status when compared with placebo.[140] Similarly, a 12-month intervention of daily spironolactone did not result in CRF improvement.[141] More recently, novel interventions aimed at enhancing the nitric oxide signaling pathway to increase its bioavailability have been tested in clinical trials. However, despite promising results in small pilot studies, a 4-week intervention of inhaled inorganic nitrite (a precursor to nitric oxide) did not improve CRF in patients with HFpEF.[142] Although an effective pharmacological intervention to manage HFpEF has not been found, future studies are encouraged to continue to use CRF as a primary outcome of interest.

Among the traditional risk factors for CVD, CRF has consistently shown to be one of the strongest prognosticators. A greater CRF in men with the metabolic syndrome protects against all-cause and CVD mortality to similar to what is seen in healthy men.[143] In addition to investigating the effects of CRF in patients with metabolic syndrome, the relation between CRF and obesity has also received much attention. As outlined by Kennedy et al,[144] the independent effects of fitness versus fatness have been debated. Several of the authors of this review, as well as others, have evaluated the independent effects of excess adiposity (ie, obesity) and CRF on subsequent CVD and all-cause mortality.[1–3,133,144–148] In fact, considerable evidence indicates the high levels of CRF significantly attenuate or even eliminates the elevated risk of CVD- and all-cause mortality in overweight and obese individuals. This has been reported in patients with dyslipidemia and T2DM as well as in the general population. Indeed, CRF markedly alters the relationship of fatness and subsequent prognosis. Recently, Barry et al[146] performed a meta-analysis on 8 studies and 9 independent groups to assess the joint impact of body mass index (BMI), a surrogate for increased adiposity, and CRF on CVD mortality. Unfit individuals had 2× to 3× higher mortality risk across all levels of BMI. Both overweight fit and obese fit had 25% and 42% increased mortality risk, respectively, compared with normal weight fit, which is considerably <2-fold increased risk reported in overweight unfit individuals.

We have recently reviewed the impact of CRF on prognosis in the obesity paradox, especially in CHD, HF, and atrial fibrillation.[2,145,147–149] The obesity paradox describes the improved prognosis typically reported in epidemiological studies in patients with class I and II obesity compared with normal weight and underweight individuals in the setting of established CVD, particularly CHD, HF, and more recently atrial fibrillation. In a study of 9563 patients with CHD followed for an average of over 13 years, those in the bottom tertile of CRF based on age and sex showed an obesity paradox. In fact, in this group of unfit individuals, measures of adiposity, such as higher BMI, % body fat, and waist circumference, were associated with improved prognosis compared with the thinner but similarly unfit individuals.[150] However, the relatively fit CHD patients (not in the bottom tertile for age- and sex-based CRF) had an excellent prognosis that was similar in all groups of adiposity, suggesting that increased BMI, % body fat, and waist circumference were no longer protective in the setting of preserved or increased CRF. Similarly, in 2066 patients with HFrEF,[151] those individuals with reduced CRF defined as peak VO_2 <14 mL/kg per minute and with concomitant obesity presented a more favorable prognosis compared with normal weight individuals. However, an obesity paradox was not reported in those patients with a relatively preserved CRF (peak VO_2 ≥14 mL/kg per minute), suggesting that in patients with HF, obesity may only be protective in the setting of reduced CRF and that perhaps therapeutics aiming at improving CRF in patients with HF may result in greater benefits as compared to those targeting body weight alone. In addition to CHD and HF, CRF levels and related improvements over time have been associated with markedly improved prognosis also in patients with atrial fibrillation.[149,152]

A recent study from Norway (HUNT study [The Nord-Trøndelag Health Study]) also demonstrated that PA levels were stronger predictors of survival compared with BMI.[153] In fact, while changes in PA markedly impacted mortality, with increased PA levels associated with an improved prognosis, changes in BMI, including weight loss, did not affect mortality rate.[154] Taken together, these data support the importance of increased CRF and PA to reduce CVD- and all-cause mortality risks, independent of obesity.

Importance of Exercise in HF

Currently, over 6 million adults have been diagnosed with HF and more sobering is the projected increase to over 8 million by the year 2030.[155] Among elderly individuals, HF-related exacerbations is the most common cause for hospitalization, placing a significant burden on individuals as well as the health care system. Exercise intolerance, typically defined as reduced CRF, is the major symptom in patients with HF.[156,157] As described above, increasing PA and ET remain the most effective therapeutic strategies to improve CRF.[1,158] ET induces improvements in CRF typically objectively assessed with peak VO_2 during a maximal cardiopulmonary exercise test[159,160] in a wide spectrum of HF phenotypes,[161] including HFrEF[162] and HFpEF.[163] The effects of ET on CRF have been tested in several small randomized controlled trials and supported by meta-analyses suggesting beneficial effects of ET on clinical outcomes.[164,165] However, the majority of these studies were performed in a single-center and limited by the small sample size, making them likely unpowered to detect meaningful improvements in strong clinical outcomes (eg, all-cause mortality and HF hospitalizations).

The largest randomized controlled trial testing the efficacy and safety of ET on clinical outcomes is the multicenter HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), which randomized >2300 stable patients with HFrEF (LVEF ≤35%) with New York Heart Association class II to IV to 36 supervised sessions of aerobic ET and home-based ET in addition to standard of care or to standard of care alone.[162] After a median follow-up of about 30 months, patients randomized to the ET group experienced a modest 4% improvement in peak VO_2[162] which was lower than the anticipated 10% to 15% suggested by the smaller studies.[166] One of the reasons for the small improvement in CRF was perhaps the low adherence to the prescribed ET, with only 30% of patients achieving the targeted level of ET in terms of recommended minutes/wk.[162] Nevertheless, the ET training failed to reduce the risk for the primary composite end point of all-cause mortality and all-cause hospitalizations. However, after prespecified statistical adjustments for key prognostic factors of morbidity, ET was associated with a significant 13% relative risk reduction for the primary composite end point as well as a 15% relative risk reduction for the composite secondary end point of CVD mortality and HF hospitalizations.[162] A secondary analysis of the trial also suggested a greater reduction for the primary and secondary composite end points in those patients who achieved the targeted goal of weekly ET which was also consistent with a greater improvement in CRF reported in this subgroup.[167] Importantly, ET was safe as the number of adverse events did not differ between the intervention and control groups.[162] Clearly, the HF-ACTION has added important information on the beneficial effects of ET, however, those were limited to HF patients with an LVEF ≤35%, and to date similar large multicenter studies in HFpEF, or even in HFrEF but with LVEF ≥35%, are lacking and, in fact, highly encouraged, perhaps this time with the use of additional tools to improve adherence to ET during the course of the study.[168] Nevertheless, ET seems to exert similar, if not even greater benefit, at least on CRF, in patients HFpEF.[163]

The improvements in CRF following ET in the different forms of HF seems to result from a variety of mechanisms.[160,169] Peak VO_2, typically reported in a milliliter of oxygen consumption per kilogram of body weight per minute (mL/kg per minute), following the Fick principle results from the product of cardiac output and arteriovenous oxygen difference [$C(a-v)O_2$], which is clearly also affected by hemoglobin concentrations:

$$\text{Peak } VO_2 = (\text{stroke volume} \times \text{heart rate})_{max} \times [C(a-v)O_2]_{max}$$

ET can, therefore, improve CRF (ie, peak VO_2) by affecting one or more of these variables.

In patients with HFrEF, in which the effects of ET have been investigated the most compared with HFpEF, the ET-induced changes in CRF have been associated with a combination of improvements in cardiac factors and peripheral noncardiac factors,[170] measured using both invasive and noninvasive assessments. In patients with HFrEF, ET can improve systolic function (ie, LVEF) and cardiac remodeling, by reducing LV end-diastolic volume and LV end-systolic volume,[171] finally resulting in improved peak cardiac output.[172] Importantly, the improvement in CRF induced by ET also result from improvements in peripheral factors, particularly an increase in systemic arterial-venous oxygen difference, leg blood flow, and oxygen delivery.[172] Such effects are typically independent of changes in body weight, which highlights the importance of targeting CRF in HFrEF, independent of changes in body mass.

In addition to ET, several pharmacological strategies have also shown improvements in CRF in HFrEF[173] leading to larger CVD outcomes trials investigating the effects on clinical outcomes of such therapies. However, as described in the prior sections of this review, several failures in HFpEF have been reported in the last years as well as many efficacy, design, and ethical issues that have been associated with exploring advanced therapies that involve stem cell interventions.[174] Such disappointing results have increased the attention on the effects of ET in this population. Indeed, ET alone is perhaps the most powerful tool to improve CRF in HFpEF, particularly when combined with weight loss strategies (ie, caloric restriction) in patients with concomitant obesity.[175] The mechanisms of improvements in CRF mediated by ET, however, differ significantly from what described previously in HFrEF. A meta-analysis of 6 randomized controlled trials investigating the effects of ET in HFpEF found that ET improves CRF but without significantly affecting cardiac systolic and diastolic function.[163] Such results suggest that noncardiac limitations may be major contributors for exercise intolerance in HFpEF. Few studies have confirmed that ET training improves CRF in older patients with HFpEF[176] but without inducing significant changes in resting and peak cardiac output and cardiac index, proposing improvements in peak $C(a-v)O_2$ as major contributors for improved CRF in this population.[171] Prior small studies, however, have shown some degree of improvements in cardiac diastolic function in patients with HFpEF.[177] Clearly, the lack of a universal definition of HFpEF plays a major role in determining potential improvements in cardiac versus noncardiac factor, or perhaps a combination of both. The presence of cardiac diastolic dysfunction, particularly when assessed invasively and during exercise,[178–181]

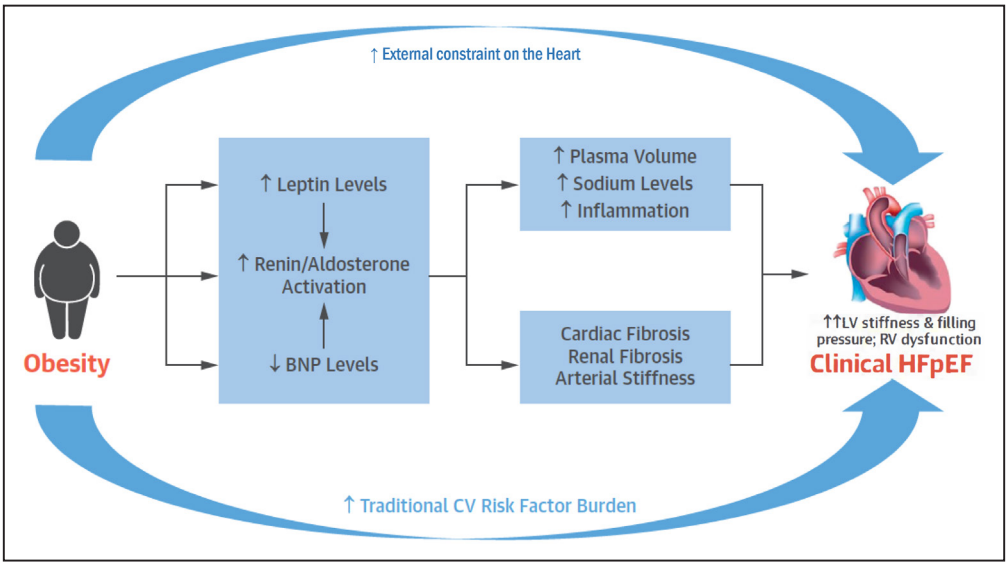

Figure 3. Proposed mechanisms by which obesity can contribute towards the development and progression of heart failure with preserved ejection fraction (HFpEF). BNP indicates B-type natriuretic peptide; CV, cardiovascular; LV, left ventricular; and RV, right ventricular. Adapted from Pandey et al[184] with permission. Copyright ©2018, Elsevier.

may identify those patients in which ET could affect cardiac function to a greater degree compared with those who have been diagnosed with HFpEF, but without meeting major diastolic dysfunction criteria for the initial HFpEF diagnosis.[182] HFpEF is a highly heterogeneous population, to the extent that different phenotypes of HFpEF have been proposed in the literature.[183] Individuals that gain weight over time have been shown to have increased diastolic stiffening,[184,185] which may partly explain the high prevalence of obesity found in patients with HFpEF (Figure 3). Obese HFpEF patients have an increased plasma volume, greater degree of concentric LV remodeling and right ventricular dilation, more right ventricular dysfunction,[186] higher biventricular fillings pressures during exercise, and lower CRF compared with nonobese HFpEF and control individuals.[187] ET has been proven to be effective in most phenotypes and subgroups, more recently also the in patients with HFpEF who also have class II and III obesity,[175] which represent one of the most common comorbid condition in this population and in which adiposity[188,189] and peripheral noncardiac factors[176] have been recognized as major determinants of reduced CRF. Initiating ET before the development of HFpEF would certainly be an effective way to reverse the deleterious effects of a sedentary lifestyle.[190]

Patients with HF are also characterized by reduced subjective assessment of quality of life, typically measured using validated questionnaires.[191] ET is an effective strategy to improve quality of life in both HFrEF[192] and HFpEF,[193] further supporting the importance of its implementation in the care of patients with HF.[193]

Importance of Exercise in Muscular Fitness

Body composition compartments play a central role in determining CRF.[189,194–196] Particularly, the levels of lean mass (LM) of the extremities (ie, appendicular LM) are considered the best surrogate for appendicular skeletal muscle mass,[197] major determinant of CRF.[198] In addition to the amount of LM, its composition and functionality are also important. Recently, the ratio between intermuscular fat and skeletal muscle mass area assessed with magnetic resonance imaging was found to be the strongest predictor for exercise intolerance in patients with HFpEF.[194] Furthermore, when a reduced amount of LM is associated with reduced functionality, patients typically present with sarcopenia,[197] which has been associated with worse CRF and outcomes in several chronic diseases, recently also in HF.[199] When sarcopenia is coupled with excess adiposity (ie, obesity), it can be defined as sarcopenic obesity, which is associated with an even worse CRF compared with sarcopenia alone.[189,200,201] For such reasons, preserving or perhaps even increasing LM with resistance training in association with aerobic exercise may represent the most effective therapeutic strategy to improve muscular fitness in the setting of HF.[202,203] This may be particularly true in older adults, in which LM loss occurs physiologically, therefore, increasing the risk of sarcopenia and sarcopenic obesity, but also in the more advanced stages of HF, which are characterized by the presence of a systemic catabolic state responsible for the loss of LM, often associated with concomitant loss of FM, which is, when unintentional, a critical negative prognostic factor in HF.[203,204] Randomized trials testing these hypotheses and also investigating the intensity of the resistance ET in association with more established protocols involving aerobic ET are clearly needed.

Exercise Dosing

There continues to be considerable controversy about the optimal dose of PA/ET for CVD and general prevention; however, substantial evidence suggests that any level of PA/ET is better than none.[1–3,133,205] Physical Activity Federal Guidelines call for a minimum of 150 minutes per week of moderate aerobic PA or 75 minutes per week of vigorous PA, while the Institute of Medicine suggests that 60 minutes daily of total PA is ideal.[1,2,7,19,160] The majority of the general population does not meet these guidelines, with only 10% meeting these minimum recommend level of PA using objective assessments, such as

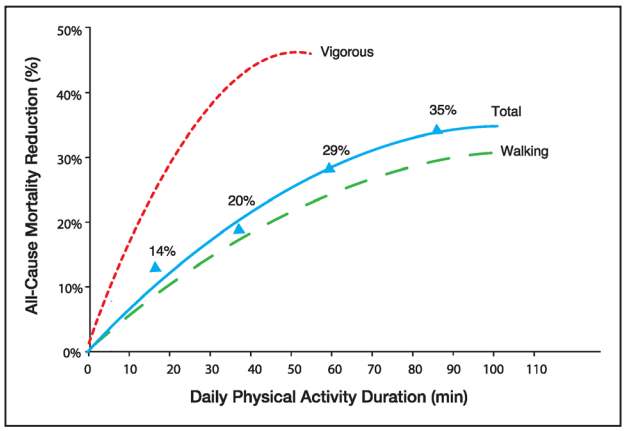

Figure 4. Daily physical activity duration and all-cause mortality reduction. Reprinted from Wen et al[59] with permission. Copyright ©2011, Elsevier.

accelerometers.[1,2,206,207] However, recent evidence indicates substantial benefits even with ET doses much lower than what recommended in these guidelines.

In a large study of 416 175 individuals from Taiwan, Wen et al[59] noted a dose-response relationship between aerobic PA and subsequent mortality, with some mortality reductions noted with just 15 minutes per day of moderate PA (Figure 4). In fact, progressive reductions in mortality were noted up to ≤90 daily minutes of moderate PA and ≤30 to 40 minutes of vigorous PA, which was defined as only 6.5 to 8.5 METs. In a recent large running study from 55 000 people from the Aerobics Center Longitudinal Study, including 13 000 runners and 42 000 nonrunners, who were followed on average for nearly 15 years, runners had impressive reductions in mortality and CVD mortality by 30% and 45%, respectively, compared with nonrunners, with an average increase in life expectantly and CVD life expectancy of 3 and 4.1 years, respectively.[27] Persistent runners had the full benefits, while those who had stopped running or started running during the study had nearly half the benefits compared with never runners. These results are not unexpected, and many would believe that there are benefits of running but also there may be selection bias, in that those able to run may be healthier than nonrunners.

However, interesting findings emerge when assessing running dosing, by dividing runners into quintiles (Q) of exercise volumes, such as miles per week, times per week and minutes per week. In fact, Q1 runners (<6 miles per week, 1–2 times per week, and <51 minutes per week) had similar all-cause and CVD-mortality risks compared with Q2–Q4 runners, with a slight trend to lower mortality to Q5 runners (Figure 5).[27] These results suggest that weekly running, which is often considered to be a relatively high intensity form of

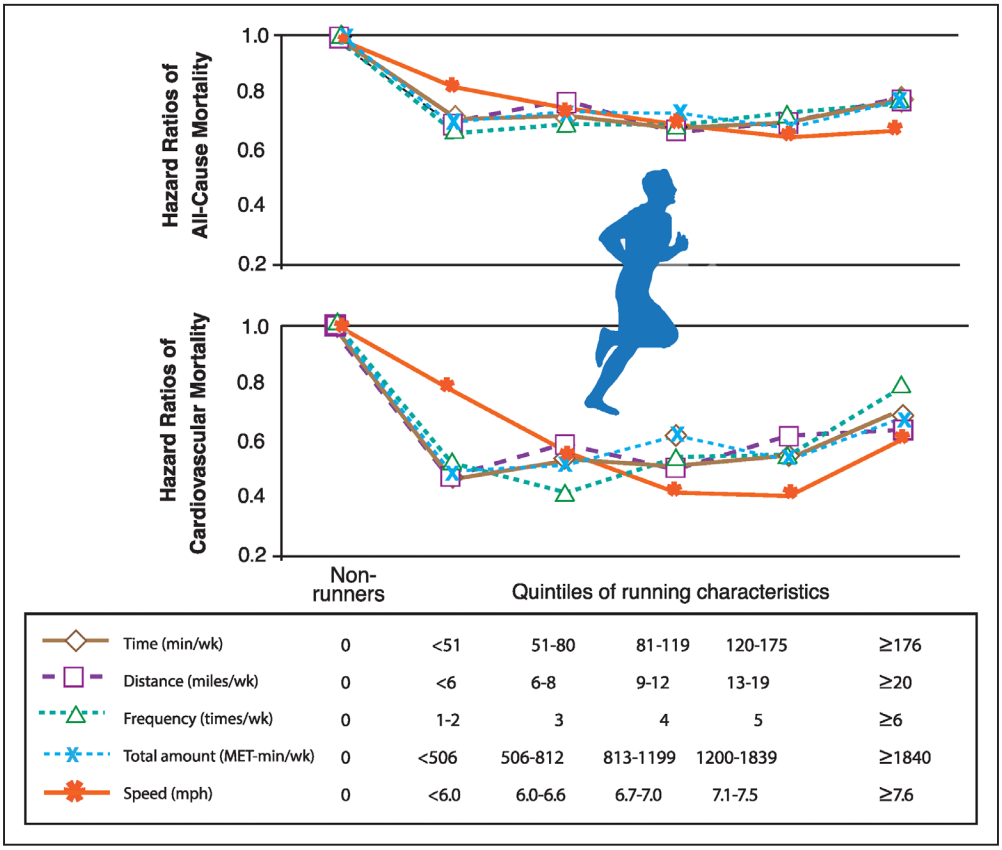

Figure 5. Hazard ratios (HRs) of all-cause and cardiovascular mortality by running characteristic (weekly running time, distance, frequency, total amount, and speed). Participants were classified into 6 groups: nonrunners (reference group) and 5 quintiles of each running characteristic. All HRs were adjusted for baseline age (y), sex, examination year, smoking status (never, former, or current), alcohol consumption (heavy drinker or not), other physical activities except running (0, 1–499, or ≥500 metabolic equivalent [MET] minutes/wk), and parental history of cardiovascular disease (yes or no). All *P* values for HRs across running characteristics were <0.05 for all-cause and cardiovascular mortality except for running frequency of ≥6 times/wk (*P*=0.11) and speed of <6.0 miles per hour (*P*=0.10) for cardiovascular mortality. Reprinted from Lee et al[27] with permission. Copyright ©2014, Elsevier.

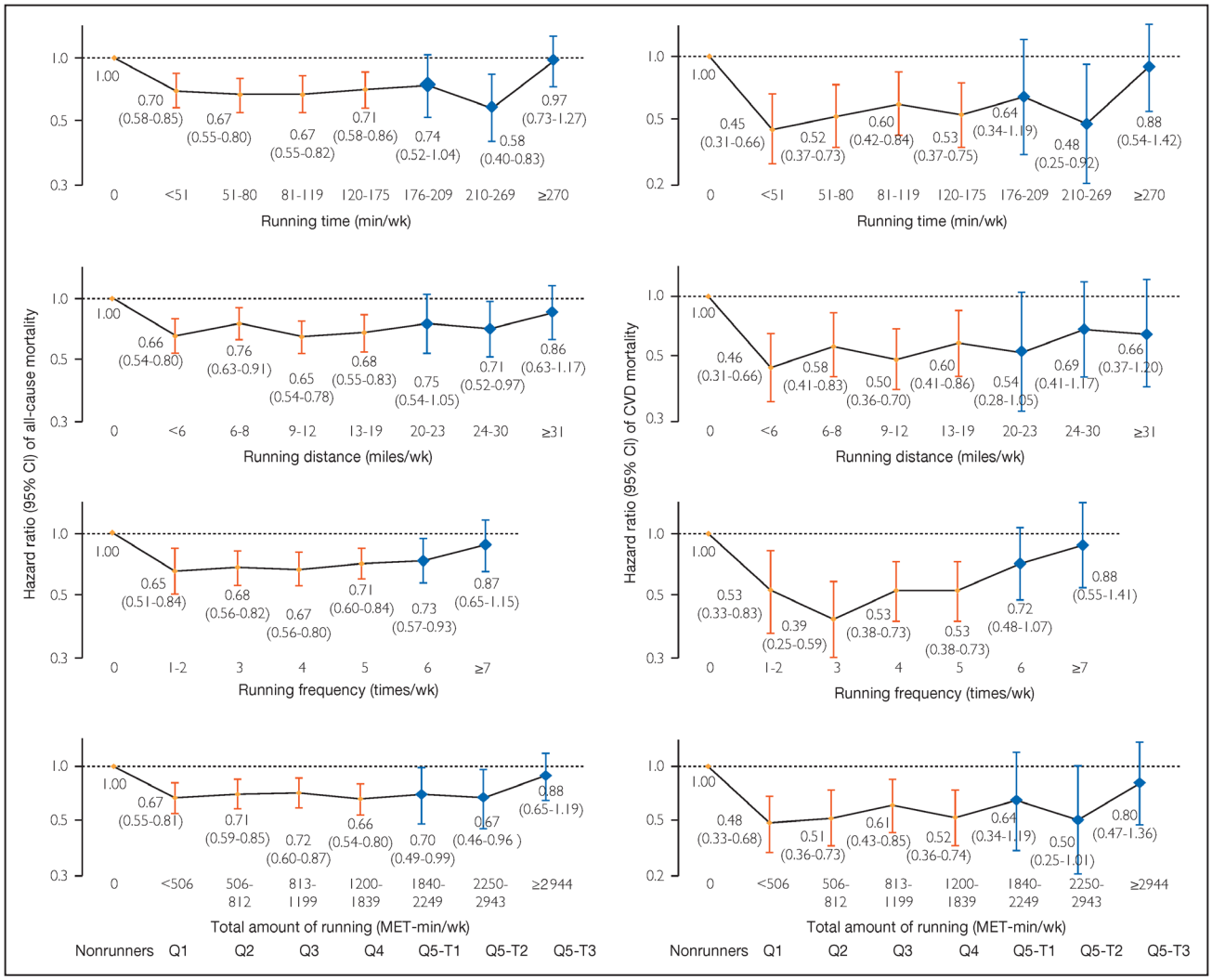

Figure 6. Hazard ratios (HRs) of all-cause and cardiovascular disease (CVD) mortality by weekly running time, distance, frequency, and total amount. Participants were classified into 8 groups: nonrunners and 5 quintiles of each running dose (Q1–Q5) with the last quintile (Q5) additionally categorized into 3 tertiles (Q5-T1, Q5-T2, and Q5-T3) using larger markers (7 groups for running frequency because of limited numbers in ≥7 times/wk). All HRs were adjusted for baseline age (y), sex, examination year, smoking status (never, former, or current), alcohol consumption (heavy drinker or not), other physical activities except running (0, 1–499, or ≥500 metabolic equivalent task minutes per week [MET min/wk]), and parental CVD (yes or no). The number of participants (number of all-cause deaths) were 42 121 (2857), 2710 (110), 2584 (116), 2505 (103), 2647 (112), 850 (33), 822 (30), and 898 (52) in the corresponding 8 running time groups from nonrunners to Q5-T3; 42 121 (2857), 2626 (105), 2473 (120), 2961 (123), 2218 (92), 885 (36), 1027 (40), and 826 (40) in running distance; 42 121 (2857), 2757 (62), 3076 (105), 2817 (131), 2500 (143), 1215 (66), and 651 (49) in running frequency; and 42 121 (2857), 2609 (109), 2598 (122), 2558 (116), 2626 (105), 863 (31), 886 (30), and 876 (43) in total running amount. The number of participants (number of CVD deaths) were 40 319 (1055), 2628 (28), 2501 (33), 2435 (33), 2567 (32), 827 (10), 801 (9), and 863 (17) in the corresponding 8 running time groups from nonrunners to Q5-T3; 40 319 (1055), 2550 (29), 2386 (33), 2874 (36), 2156 (30), 858 (9), 1001 (14), and 797 (11) in running distance; 40 319 (1055), 2714 (19), 2993 (22), 2725 (39), 2396 (39), 1174 (25), and 620 (18) in running frequency; and 40 319 (1055), 2531 (31), 2508 (32), 2477 (35), 2553 (32), 842 (10), 864 (8), and 847 (14) in total running amount. The bars indicate 95% CIs, and HRs appear next to the bars. Reprinted from Lee et al[208] with permission. Copyright ©2016, Elsevier.

ET that is common and convenient, the maximal benefits on all-cause and CVD-mortality occurred at low doses, including ET doses well below the current International PA guidelines. In a subsequent analysis of the Q5 runners who were divided into tertiles, the top 8% of runners with regards to dosing appeared to lose the benefits, at least compared with the lower dose runners (Figure 6),[208] suggesting that more may not be better but also raising the possibility that more could be worse with regard to ET dosing.

Future Considerations

Although the benefits of PA/ET and deleterious effects of SB/PI are well established, further study on potential benefits of ET on major clinical events in HFpEF, T2DM, and other chronic diseases is needed. Similarly, the relative values of high-intensity interval training and resistance training on major clinical events in these populations may also need further investigation.[209] Additionally, much of our limited understanding of the mechanistic consequences of SB derives from preclinical models and cross-sectional examinations of sedentary individuals. Efforts have recently been made to characterize the effects of prolonged acute (ie, hours) sitting on metabolic parameters such as postprandial glucose and insulin responses, however, no study has examined the cellular and molecular responses in various tissues across different populations and PA status. Another area that warrants attention is elucidating the

high degree of interindividual variation in CRF responses to exercise interventions. Ross et al[103] have made great strides in addressing the influence of amount and intensity on CRF outcomes, however, there still remains a large gap in identifying molecular characteristics that may provide insight into who responds or does not respond to exercise. Finally, we should recognize that the PA/ET fields of medicine have not done an excellent job of promoting PA/ET throughout the world and in many diseases, including the patients with CVD.However, we highly encourage research investigating novel strategies to improve adherence to the recommendations described above, finally resulting in increased PA/ET and reduced SB/PI across the globe.[2,210]

Conclusions

In this State-of-the-Art review, we discussed the potential benefits of PA/ET and the adverse effects of SB/PI in the primary and secondary prevention of chronic diseases, especially CVD. The constellation of data reviewed in this article marked the benefits of increased PA/ET, particularly as they lead to increased CRF, finally resulting in improved prognosis in a large spectrum of metabolic diseases and CVD. Greater implementation of this therapy, therefore, is desperately needed worldwide.

Disclosures

None.

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