Exercise at the Extremes: The Amount of Exercise to Reduce Cardiovascular Events

A Clinical Perspective Document from the ACC Sports and Exercise Cardiology Leadership Council

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Abstract:

Habitual physical activity and regular exercise training improve cardiovascular health and longevity. A physically active lifestyle is therefore a key aspect of primary and secondary prevention strategies. An appropriate volume and intensity are essential to maximally benefit from exercise interventions. This document summarizes available evidence on the relationship between the exercise volume and risk reductions in cardiovascular morbidity and mortality. Furthermore, the risks and benefits of moderate- *versus* high-intensity exercise interventions are compared. Findings are presented for the general population and cardiac patients eligible for cardiac rehabilitation. Finally, the controversy of excessive volumes of exercise in the athletic population is discussed.

KEYWORDS: Physical activity, Health, Longevity, Mortality, Coronary Artery Disease, Myocardial Infarction, Heart Failure, Cardiac Patients, Athletes.

Abbreviations

CAC	coronary artery calcification
CI	confidence interval
CVD	cardiovascular disease
HR	hazard ratio
IQR	inter quartile range
LGE	late gadolinium enhancement
METs	metabolic equivalent of task score
MI	myocardial infarction
HIIT	high intensity interval training
MICT	moderate intensity continuous training
OR	odds ratio
QOL	quality of life
RR	risk ratio
SCD	sudden cardiac deaths

1.0 Introduction:

Habitual physical activity and exercise training reduce cardiovascular disease (CVD) morbidity and mortality (1,2). The 2008 Physical Activity Guidelines Advisory Committee Report recommended 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic exercise for all US adults (Table 1) since this exercise volume provides significant health improvements for most people much of the time. However, only half of Americans meets these guidelines (3). On the other hand, participation in endurance exercise races has grown in popularity among the most active individuals as demonstrated by the marked increase in the number of participants in marathons, triathlons and cycling races over the past 3 decades (4,5). These individuals typically engage in aerobic exercise volumes and intensities well above the 2008 guideline recommendations. Several recent reports surprisingly suggest that high volumes of aerobic exercise may be as bad for CVD outcomes as physical inactivity (6-9). The public media has embraced the idea that exercise may harm the heart and disseminated this message, thereby diverting attention away from the benefits of exercise as a potent intervention for the primary and secondary prevention of heart disease (10). This document will review the literature on the volume and intensity of aerobic exercise required for favorable cardiovascular health, and also address the question as to whether or not there is a volume that increases CVD risk.

Table 1. Examples of moderate- and vigorous-intensity activities to achieve 2008 exercise guideline recommendations (11).

Moderate-intensity aerobic activities >150 min/week	**Vigorous-intensity aerobic activities** >75 min/week
Brisk walking (>3 miles/hour)	Uphill walking or race walking
Bicycling (< 10 miles/hour)	Bicycling (> 10 miles/hour)
Water aerobics	Running or jogging
Tennis (doubles)	Tennis (singles)

Ballroom dancing	Aerobic dancing
General gardening	Heavy gardening (digging / hoeing)

2.0 Exercise in primary prevention

2.1 General Benefits of Exercise

The health benefits of exercise have been recognized since the epidemiological studies of Morris and colleagues who in the 1950's reported lower rates of coronary heart disease among the conductors of London's double-decker busses compared to the drivers (12). Morris and colleagues also reported a lower incidence of coronary heart disease among English postmen compared to telephone operators working at the same company (12). These data were the first to illustrate an association between habitual physical activity and cardiovascular health. Many subsequent epidemiological studies confirmed this inverse relationship between physical activity and CVD (13-15), but none have proven causation because all such studies are observational. To date, there are no randomized clinical trials directly testing whether physical activity prevents CVD. Such a study would require an enormous sample size and study duration because of subject cross-over among those volunteering for an "exercise study" and because the progressively lower rates of primary CVD in the general population would reduce CVD endpoints. Powell *et al.* (16) evaluated the possibly causative relationship between physical activity and cardiovascular disease using the same criteria used to document a causative relationship between cigarette smoking and health (17), a relationship also lacking a randomized, controlled clinical trial. They demonstrated that the relationship between physical activity and CVD was strong, consistent among studies, with a graded risk reduction with increasing exercise volumes, and was coherent with clinical studies showing a putatively beneficial effect of exercise on

CVD risk factors (16). They concluded that increasing physical activity was causally related to lower rates of CVD despite the absence of the classical clinical trial.

The CVD benefits of exercise are likely mediated via multiple mechanisms (Central illustration). Regular exercise training improves the CVD risk profile by reducing triglycerides and increasing HDL-cholesterol (18), lowering blood pressure (19), improving glucose metabolism and insulin sensitivity (20), reducing body weight, and reducing inflammatory markers (21). These risk factor improvements explain 59% of the reduction in CVD (22). The remaining 41% may result from improved endothelial function (23), enhanced vagal tone producing lower heart rates (24), vascular remodeling including larger vessel diameters and an enhanced nitric oxide bioavailability.

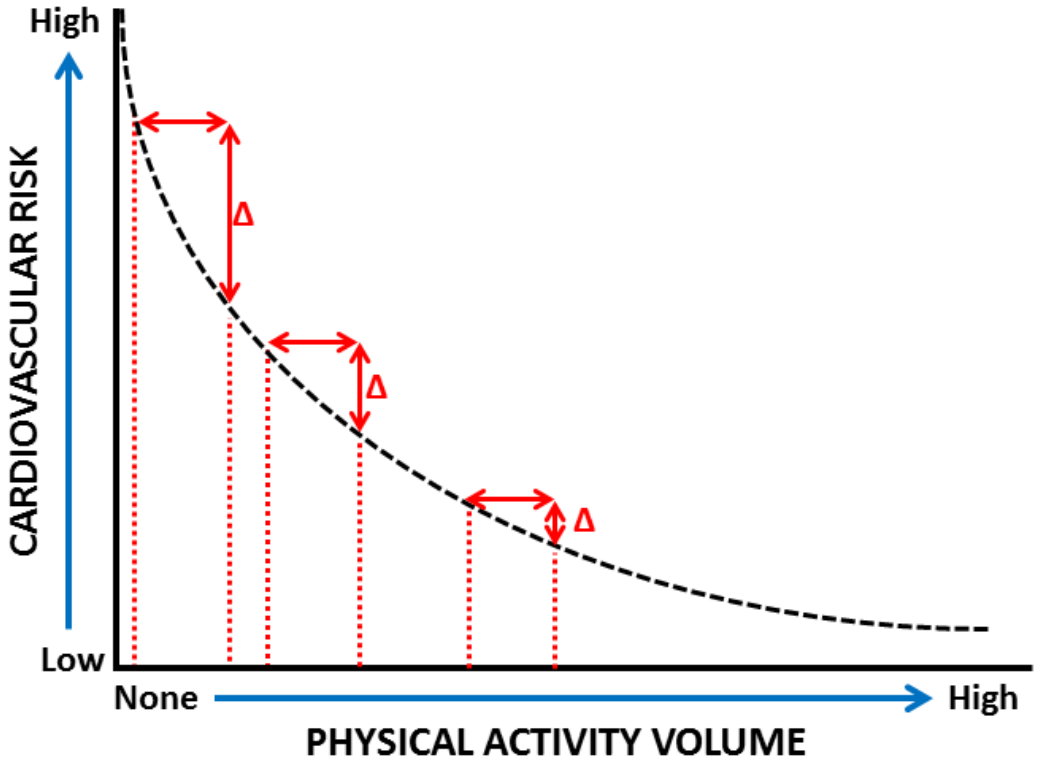


Figure 1: The curvilinear relationship between physical activity and cardiovascular risk. A similar increase in physical activity yields different risk reductions across the activity spectrum. Physical inactivity is associated with the highest risk, whereas high aerobic exercise volumes are associated with the lowest risk (25).

2.2 Dose-response relationship between physical activity and mortality

The association between exercise or physical activity and CVD outcome is most frequently described as a curvilinear relationship (Figure 1) (25). This indicates that a change from an inactive to a mild or moderately active lifestyle yields a relatively large risk reduction, whereas further increasing exercise volumes produce smaller risk reductions. Thus, any physical activity is better than none, though higher volumes, even above the 2008 guideline recommendations, appear to further reduce CVD.

Several studies have examined the minimum volume of aerobic physical activity required to produce health benefits. The least active, but still effective, behavior is standing. Standing >2 hours/day is associated with a 10% reduction of all-cause mortality (HR 0.90, CI 0.85-0.95) compared to standing <2 hours/day (26). Increased standing time was associated with larger risk reductions, with the lowest mortality in individuals standing ≥8 hours/day (HR 0.76, CI 0.69-0.95), but standing time could have also included light physical activity, such as walking, in addition to only standing. The study population included 221,240 Australians aged ≥45 years and the results were independent of health status and were not altered by sex, age, BMI, other physical activity and sitting time (26). Similar reductions in all-cause mortality with standing were observed prospectively in 16,586 Canadians (27), but this study also showed that standing 25% and 75% of the time was associated with 18% and 32% reductions in CVD mortality, respectively (HR 0.82, CI 0.68–0.99 and HR 0.68, CI 0.50–0.92) (27). This dose-response relationship between standing and CVD mortality informs on the lower end of the CVD benefit relationship and supports the concept that even small amounts of physical activity provide CVD benefit.

An additional benefit of the increase in time standing and performing light physical activity is the simultaneous reduction of even less taxing activities such as sitting. Prolonged

sitting increases the risk for all-cause mortality in a dose-dependent fashion (28). Importantly, the detrimental effects of sitting appear to be independent from the benefits of physical activity (29). Recent studies demonstrate that breaking up sitting time improve cardiovascular health (30) and glucose homeostasis (31), and replacement of sitting time effectively reduces all-cause mortality (32). It is therefore recommended that future primary intervention programs target both, sedentary behavior as well as habitual physical activity, to maximize the reduction in cardiovascular risk.

Studies of moderate- and vigorous-intensity activity below the recommended exercise volume (33-35) confirm substantial health benefits from low levels of activity. Americans running 51 min/week or 68% of the recommended volume experienced lower CVD mortality (HR 0.45, CI 0.31–0.66) and all-cause mortality (HR 0.70, CI 0.58–0.85) compared to nonrunners (33). Similarly, Taiwanese exercising 92 min/week or 61% of the recommended volume experienced a reduction in CVD mortality (HR 0.81, CI 0.71–0.93) and all-cause mortality (HR 0.86, CI 0.81–0.91) compared to their inactive peers (34). A meta-analysis including 661,137 American and European men and women also demonstrated that individuals performing moderate- to vigorous-intensity leisure time physical activity at a volume below 2008 guideline recommendations had a 20% reduction in CVD mortality (HR 0.80, CI 0.77-0.84) and all-cause mortality (HR 0.80, CI 0.78-0.82) compared to inactive controls (35). These data emphasize that even low exercise volumescan effectively reduce CVD mortality, a message that clinicians should communicate to stimulate vulnerable populations to become physically active.

Determining the maximal volume of aerobic exercise to improve CVD outcomes is difficult because it requires measuring the frequency, duration and intensity of exercise training. The Metabolic Equivalent of Task (MET) score uses the intensity of exercise (a

multiple of the resting metabolic rate) from the Compendium for Physical Activities (36) multiplied by an assessment of the frequency (sessions/week) and duration (hours/week) to calculate the exercise volume in MET-hours/week. We combined data from Taiwanese (34), American and European population studies (35) to assess the dose-response relationship between physical activity and CVD mortality (Figure 2). Maximal risk reduction for cardiovascular mortality was found at a volume of 41 MET-h/week. This is 3.5 to 4 times greater than the recommended volume and equals 547 min/week of moderate-intensity exercise at 4.5 METs or 289 min/week of vigorous-intensity exercise at 8.5 METs. Individuals performing exercise at this volume experienced a 45% lower risk for CVD mortality (HR 0.55, CI 0.46-0.66) compared to inactive controls.

Only 3.5% of individuals included in the meta-analysis mentioned exceed the exercise volume that was associated with maximal health benefits (35). These individuals experienced reductions in CVD mortality comparable to the 'maximal benefit' group (HR 0.61, CI 0.55-0.67 and HR 0.71, CI 0.56-0.91 for subjects performing 40-75 MET-h/week and >75 MET-h/week respectively) (35) but this difference was not statistically significant in part because the small percentage of individuals exercising at this volume creates large confidence intervals. Performing exercise volumes at the upper end of the physical activity spectrum therefore appear safe since there is no evidence for adverse CVD outcomes amongst these individuals.

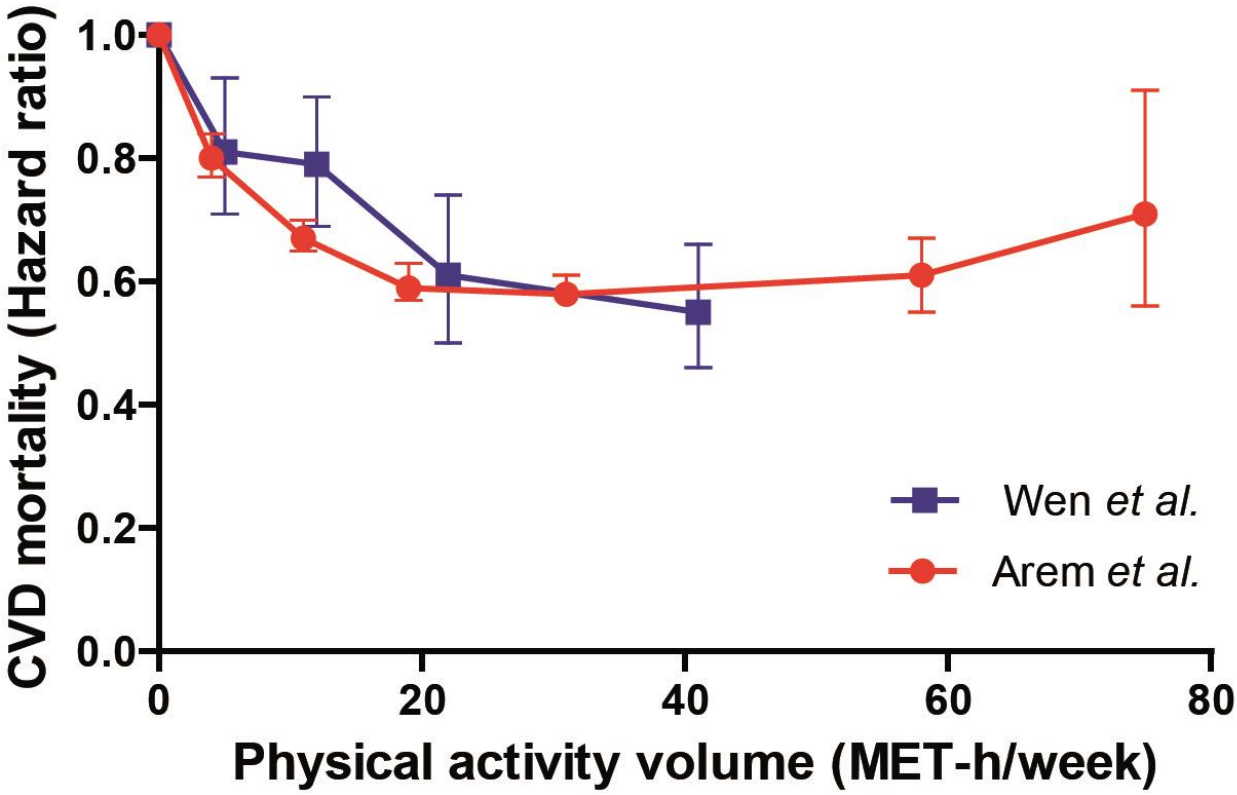


Figure 2: The dose-response curve of physical activity and cardiovascular mortality based on data from the studies of Wen *et al* (blue squares) (34) and Arem *et al* (red circles) (35). The average exercise volume (MET-h/week) was calculated for the ranges of physical activity that were provided in the study by Arem *et al*. The maximal risk reduction for cardiovascular mortality was found at an exercise volume of 41 MET-h/week.

2.3 Does intensity matter?

Moderate-intensity activities are defined as requiring 3.0 to 5.9 METs of energy expenditure whereas vigorous intensity requires ≥6.0 METs. High-intensity interval training produces larger improvements in cardiorespiratory fitness, expressed as VO_{2max}, compared to moderate-intensity, continuous training (37). Higher fitness levels are associated with a reduction in CVD (38) and all-cause mortality (39) in a curvilinear fashion. The potential superior health benefits of vigorous-intensity exercise are supported by epidemiological data. Australians performing <30% of their total physical activity in vigorous exercise as well as those performing >30% had reduced mortality rates compared to individuals performing only moderate-intensity exercise (HR 0.91, CI 0.84-0.98 and HR 0.87, CI 0.81-0.93 respectively)

after adjusting for total volume of moderate-to-vigorous-intensity activities (40). These observations are consistent with a systematic review of epidemiological studies and clinical trials demonstrating a larger reduction in CVD events and improvement in CVD risk factors for vigorous *versus* moderate intensity physical activity (41).

Interestingly, the dose-response curve between physical activity and mortality appears to be different for moderate *versus* vigorous intensity exercise (Figure 3). Increasing levels of moderate intensity physical activity progressively reduces CVD mortality, whereas the response curve flattens for vigorous physical activity in excess of 11 MET-h/week (33,34). Similar patterns exist for all-cause mortality, although the differences between moderate and vigorous intensity activity were less pronounced (33-35) (Figure 3). These findings indicate that increasing volumes of moderate intensity exercise are associated with further improvements in CVD health, whereas for vigorous intensity, lower volumes are associated with maximal risk reduction.

This relationship may be due at least in part to the repeated observation that vigorous intensity exercise acutely, albeit transiently, increases CVD events (42-44). A total of 122 sudden cardiac deaths (SCD), 23 (18.9%) exercise related, occurred in a study of 21,481 male physicians (44). The absolute risk for a vigorous exercise related SCD was low at 1 per 1.42 million hours, but 16.9% higher (CI 10.5 to 27.0%, $p<0.001$) than that during low/no physical activity. Despite this *acute* increase in risk during vigorous activity, the relative risk (RR) for SCD decreased progressively with increasing habitual vigorous exercise from a RR of 74.1 for those exercising vigorously <1 session/week (CI 22.0-249) *versus* a RR of 18.9 for those exercising vigorously 1-4 sessions/week (CI 10.2-35.1) *versus* a RR of 10.9 for those exercising vigorously ≥5 sessions/week (CI 4.5-26.2) (44). The pattern is similar for the association between vigorous exertion and acute myocardial infarction (MI) in the general

population (43). Among 1228 MI patients, the risk for a vigorous activity induced MI was markedly lower for individuals regularly involved in vigorous activities (≥5 sessions/week, RR=2.4) compared to sedentary individuals (no sessions/week, RR=107) (43). Such results demonstrate that vigorous physical activity transiently increases the risk for acute cardiac events, but reduces the overall risk.

In summary, volumes of moderate and vigorous intensity exercise below the 2008 Physical Activity Guideline recommendations result in a significantly lower mortality risk in different populations around the globe. Increasing volumes of moderate intensity exercise result in larger reductions of CVD mortality, whereas no further reduction in CVD mortality is observed for volumes of vigorous intensity exercise beyond 11 MET-h/week. Finally, there is no evidence for an upper limit of exercise-induced health benefits. Every volume of moderate and vigorous intensity aerobic exercise results in a reduction of all-cause and CVD mortality compared to physical inactivity.

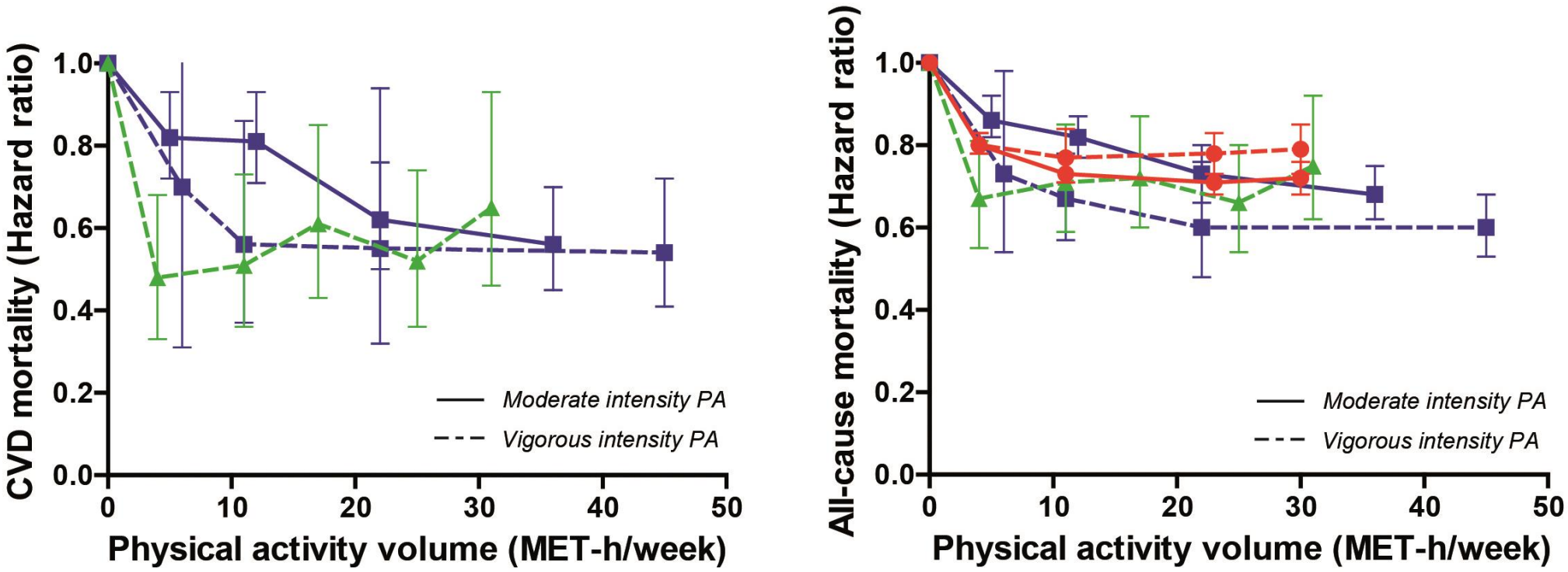


Figure 3: The dose-response curve of moderate-intensity (solid lines) and vigorous-intensity (dashed lines) physical activity and cardiovascular mortality (left panel) and all-cause mortality (right panel) based on data from the studies of Wen *et al* (blue squares) (34), Lee et al (green triangles) (33) and Arem *et al* (red circles) (35). The average exercise volume(MET-h/week) was calculated for the ranges of physical activity that were provided in the study by Arem *et al*. These figures demonstrate that vigorous intensity activities already reach a maximum risk reduction at lower exercise volumes, whereas larger volumes of moderate intensity activities are associated with a further reduction in cardiovascular/all-cause mortality.

3.0 Exercise in secondary prevention

3.1 Current Guideline Recommendations

Exercise is a key component in the management of patients with most established CVD because it reduces recurrent CVD events. Guidelines from the American College of Cardiology and American Heart Association include specific recommendations for diverse populations of cardiac patients (Table 2) (45-49). The recommend exercise volumeis generally similar to that for healthy adults: 30-60 min/day of moderate intensity aerobic activities. Exercise can be performed as a part of a clinical rehabilitation program (see paragraph 3.2) or at home and in the community. Patients are advised to include resistance exercise training to maintain strength and muscle mass. A meta-analysis of 504 studies suggests that the combination of aerobic and resistance exercise produces greater reductions in body fat and improvements in muscle strength compared to aerobic exercise alone (50). Adding strength training to aerobic programs tends to produce larger increases in cardiopulmonary fitness and improvements in quality of life (QOL) in patients with CVD (50). Increased QOL may occur because the increases in exercise capacity and strength increase self-confidence and independence after a CVD event.

Table 2. Physical activity and/or exercise recommendations for cardiac patient populations.

Recommendations for cardiac patient populations	Class of Recommendation	Level of Evidence
Congenital heart disease (45)		
Exercise prescription, guidelines for exercise, and athletic participation for patients with CHD should reflect the published recommendations of the 36th Bethesda Conference report.	I	C
Heart failure (46)		
Exercise training (or regular physical activity) is recommended as safe and effective for patients with heart failure who are able to participate to improve functional status.	I	A
Cardiac rehabilitation can be useful in clinically stable patients with heart failure to improve functional capacity, exercise duration, health-related quality of life, and mortality.	IIa	B
Non-ST-Elevation acute coronary syndromes (47)		
All eligible patients with non-ST-elevation acute coronary syndromes should be referred to a comprehensive cardiovascular rehabilitation program either before hospital discharge or during the first outpatient visit.	I	B
Detailed instructions for daily exercise, patients should be given specific instruction on activities (eg, lifting, climbing stairs, yard work, and household activities) that are permissible and those to avoid. Specific mention should be made of resumption of driving, return to work, and sexual activity.	I	B
ST-Elevation myocardial infarction (48)		
Exercise-based cardiac rehabilitation/secondary prevention programs are recommended for patients with STEMI.	I	B
A clear, detailed, and evidence-based plan of care that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with STEMI.	I	C

Stable ischemic heart disease (49)		
Medically supervised programs (cardiac rehabilitation) and physician-directed, home-based programs are recommended for at risk patients at first diagnosis.	I	A
For all patients, the clinician should encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%).	I	B
For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.	I	B
It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week.	IIa	C

3.2 Cardiac rehabilitation

Patients with stable angina pectoris, systolic heart failure, myocardial infarction, recent cardiac surgery or a percutaneous coronary intervention are eligible for cardiac rehabilitation. Contemporary cardiac rehabilitation programs include not only exercise training but also nutritional and psychological counseling; weight, blood pressure, lipid, and diabetes management; and smoking cessation (51). The goal is to reduce CVD risk via pharmacotherapy, improved health behavior and a physically active lifestyle.

In contrast to the available evidence for primary prevention, there are randomized clinical trials assessing the benefits of exercise training and cardiac rehabilitation on CVD in select patient populations. A Cochrane review of 47 randomized controlled trials including 10,794 coronary heart disease patients (52) demonstrated that cardiac rehabilitation reduced all-cause (RR 0.87, CI 0.75-0.99) and CVD mortality (RR 0.74, CI 0.63-0.87) after >1 year of follow-up. Furthermore, a decrease in hospital admissions was found in the cardiac rehabilitation *versus* standard care group within one year of follow-up (RR 0.69, CI 0.51-0.93). A meta-analysis including 6,111 post–myocardial infarction patients from 34 randomized controlled clinical trials showed similar results with exercise-based rehabilitation demonstrating a lowered risk for all-cause mortality (OR 0.74, CI 0.58-0.95), CVD mortality (OR 0.61, CI 0.40-0.91) cardiac mortality (OR 0.64, CI 0.46-0.88), and re-infarction (OR 0.54, CI 0.38-0.76) (53).

A Cochrane review of 33 randomized clinical trials including 4,740 patients with predominantly systolic heart failure (54) demonstrated that cardiac rehabilitation and exercise training reduced all-cause (RR 0.75, CI 0.62-0.92) and heart failure specific (RR 0.61, CI 0.46-0.80) hospitalization rates. QOL also improved more in the cardiac rehabilitation patients. All-cause mortality was not different between the exercise-based cardiac

rehabilitation and no exercise control arms at 1 year of follow-up (RR 0.93, CI 0.69-1.27), but trended toward significance in follow-up >1 year (RR 0.88, CI 0.75-1.02) (54).

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training or HF-ACTION trial examined the effect of exercise training in 2,331 patients with systolic heart failure and ejection fractions <35%. Subjects participated in 12 weeks of supervised thrice weekly exercise training followed by an at home training program. The investigators sought to enhance adherence to the home exercise by providing treadmills or stationary cycles to participants. Despite such efforts adherence to the exercise training program was low and the average increase in maximal oxygen uptake was only 0.7 mL/kg/min (IQR: –1.0 to 2.5), a value lower than most prior, smaller studies of exercise training in this population. Heart failure patients receiving exercise training had a reduced incidence of cardiovascular mortality and heart failure hospitalization compared to the non-exercise training usual care group (HR 0.87, CI 0.75-1.00) (55). After correction for highly prognostic baseline factors and heart failure etiology these findings became statistically significant (HR 0.85, CI 0.74-0.99). Patients receiving exercise training also reported an earlier and larger improvement in self-reported health status, which persisted over time (56).

3.3 The Volume and Intensity of Aerobic Exercise Training for Secondary Prevention

Most cardiac rehabilitation studies and programs used a relatively standard exercise protocol. Subjects generally exercised 3 times weekly for 30 to 40 minutes per session at heart rates equal to 60 to 85% of their maximal value or age-estimated maximal value. The risk of cardiac arrest during vigorous exercise in individuals with CVD was initially estimated at 6 to 164 times greater than their risk at rest (57). The risk of a cardiac event during contemporary cardiac rehabilitation is low, and estimated at only 1 cardiac arrest per

116,906 patient-hours of participation and 1 fatality per 752,365 patient-hours (58). These event rates apply to *supervised* cardiac rehabilitation where trained personnel can monitor symptoms and administer resuscitation if needed. Comparing the cardiac arrest and mortality rates suggests that the fatality rate would be 6-fold higher without successful resuscitation performed by the rehabilitation staff.

There are few studies examining the effect of exercise volumeon CVD outcomes in cardiac patients because most studies used standard and similar exercise training protocols. Data from the HF-ACTION trial suggest a curvilinear response between the volume of exercise and the subsequent risk for cardiovascular events during 28 months of follow-up (59). Heart failure patients performing exercise ≥ 5 MET-h/week had a higher event-free survival compared to those performing lower volumes of exercise (i.e. <1 / 1-3 / 3-5 MET-h/week). However, after correction for peak VO2 values, a J-shaped curve appeared with the largest risk reductions in patients exercising 3-7 MET-h/week, and less benefit for patients exercising ≥7 MET-h/week (59).

Several studies in CVD subjects exercising in unsupervised settings reinforce the hypothesis that high volumes of exercise may be deleterious in this patient group. The National Runners' and Walkers' Health studies of Williams *et al.* recorded the baseline exercise habits and health outcomes of 2,377 subjects who were self-identified as heart attack survivors at baseline (9). A total of 526 died over an average follow-up of 10.4 years, 71.5% due to CVD. CVD mortality decreased progressively with increasing amounts of exercise to a maximum mortality reduction of 63% in those running or walking at a volume of 38-50 MET-h/week compared to the least active group (<8 MET-h/week). In the most active exercisers, however, those running > 7.1 km a day or walking briskly > 10.7 km a day, the reduction in CVD mortality was only 12%, and not different from the least active group

(Figure 4A).

These data from Williams *et al.* show an attenuation of mortality risk reductions in patients with the highest levels of exercise. Studies by both Wannamethee and Mons also show an apparent reduction in the benefit of exercise in the most active subjects. Among 772 British coronary heart disease patients (60), lightly and moderately active patients had a significantly lower all-cause and CVD-related mortality risk compared to inactive patients, whereas moderate to vigorously active patients did not (Figure 4B). Similarly, Mons and colleagues found that among 1,038 German coronary heart disease patients (8), patients exercising 2-4 sessions/week demonstrated the lowest all-cause (7.6 per 1,000 person years) and cardiovascular mortality (4.5 per 1,000 person years) whereas higher or lower exercise frequencies were associated with higher mortality rates (Figure 4C). In contrast, Moholdt's examination of 3,504 Norwegian coronary heart disease patients observed no attenuated mortality risk reduction in the most active group (Figure 4D). These current studies are limited by their observational nature, use of self-reported activity patterns and a potential selection bias of participating subjects. The possibility that high levels of exercise attenuate the reduction in CVD events warrants additional examination because of the widespread perception that more of a good thing is better. Hence, the extrapolation of these observations is limited, and may only be of concern in a minority of patients.

Despite these concerns about the volume and intensity of exercise in CVD patients, several studies have explored strategies to optimize the effects of cardiac rehabilitation using high intensity interval training (HIIT), modeled after athletic training programs. HIIT was introduced into cardiac rehabilitation in 2007 and typically consists of a 10-min warm-up at 60-70% of peak heart rate, followed by four 4-min intervals at 90-95% of peak heart

rate, separated by 3-min active pauses at 50-70% of peak heart rate (61). The exercise session is ended by a 3-min cool-down at 50-70% of peak heart rate (Figure 5).

Heart failure patients receiving HIIT demonstrated a 46% improvement in cardiorespiratory fitness (VO_{2peak}) compared to only a 14% improvement in patients expending the same amount of energy during traditional, moderate intensity continuous training (MICT) consisting of a 47-min exercise bout at 70-75% of peak heart rate (Figure 5) (61).

A meta-analysis including 229 patients with coronary artery disease demonstrated that HIIT produced a larger increase in VO_{2peak} (weighted mean difference: 1.53 mL/kg/min, CI 0.84-2.23) compared to MICT (62). Similarly, a meta-analysis comparing changes in fitness in cardiac rehabilitations trials for heart failure that included 5,877 patients found larger improvements in VO_{2peak} for training programs using higher exercise intensities (63). Moreover, fewer heart failure patients withdrew from the studies in the highest exercise intensity groups.

The greater increase in cardiorespiratory fitness with more intense exercise training in CVD patients does not necessarily mean that the more intense training regimens will increase survival. There are also potential risks to more intense exercise in CVD patients especially if performed in the absence of trained medical personal. A comparison of adverse CVD events between MICT and HIIT in 4,846 cardiac patients revealed event rates of 1 per 129,456 and 1 per 23,182 patient-hours respectively (64). These data suggest a higher risk for adverse CVD outcomes with HIIT, but there was only one fatal cardiac arrest and two nonfatal cardiac arrests with MICT and HIIT, respectively, so there were too few events and insufficient power to compare risk.

Taken together, referral to an exercise rehabilitation program is recommended for cardiac patients since participants benefit from a reduced risk for future cardiovascular events and mortality. Supervised HIIT protocols yield larger health improvements than MICT protocols. The risk for cardiac arrest and sudden cardiac death during exercise is low but present. High-intensity activities and high weekly exercise volumes may attenuate the health benefits in cardiac patients, with risk rates returning to the level of inactive peers. Moderate intensity exercise at volumes comparable to guidelines (45-49) should therefore be recommended for cardiac patients by their clinicians to achieve maximal cardiovascular benefits.

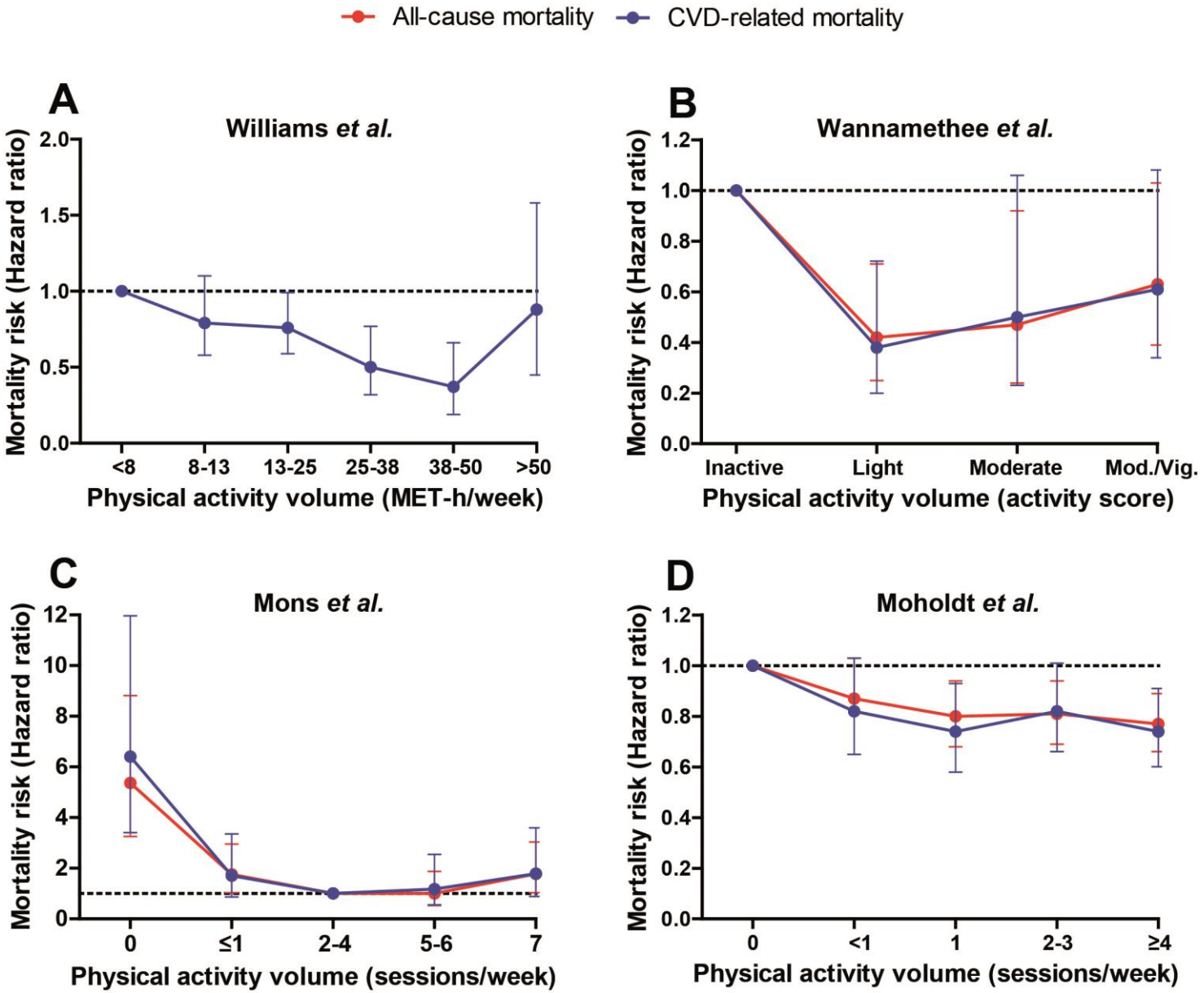


Figure 4: The dose-response curve of physical activity and all-cause (red lines) and cardiovascular mortality (blue lines) amongst cardiac patient populations. Data was extracted from the studies of A) Williams *et al* (9), B) Wannamethee *et al* (60), C) Mons *et al* (8), and D) Moholdt *et al* (65). Mod./Vig.; Moderate to vigorous.

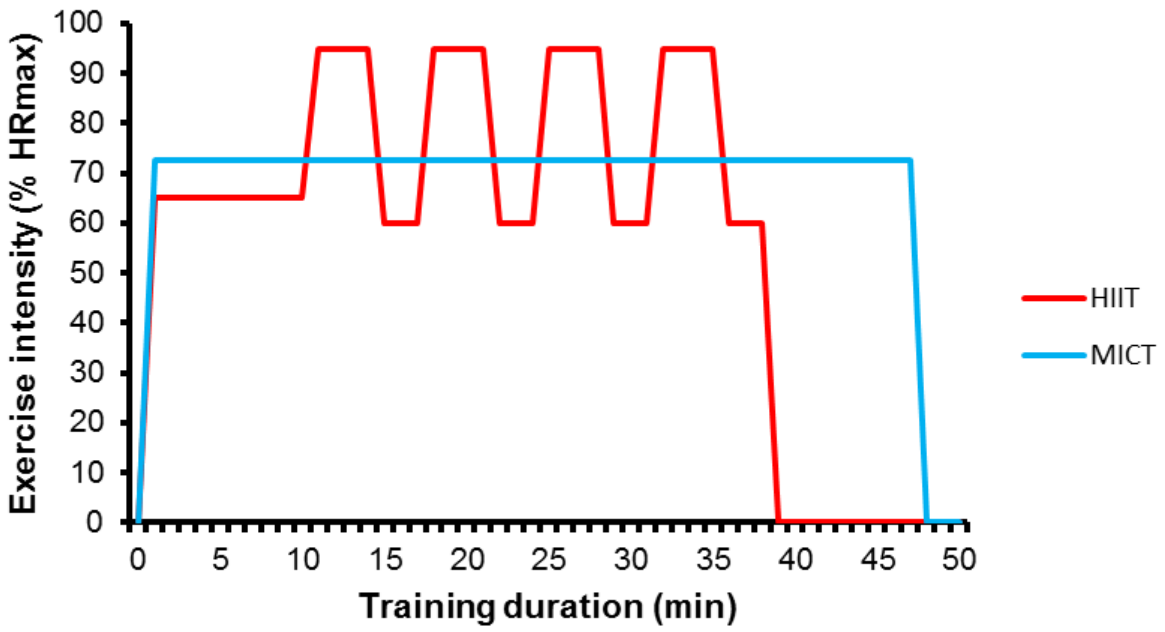


Figure 5: Example of a High Intensity Interval Training (HIIT) protocol *versus* a Moderate Intensity Continuous Training (MICT) protocol in cardiac rehabilitation. Both exercise protocols are isocaloric (61). HRmax; maximal heart rate. Min; minutes.

4.0 The controversy of excessive exercise

The amount of habitual exercise training required to be a successful endurance athlete is markedly higher than that required for cardiovascular health. Multiple studies have reported unexpected, potentially adverse cardiovascular outcomes in athletes (Central illustration). For example, some athletes demonstrate exercise induced elevations in cardiac troponin levels (66), evidence of myocardial fibrosis (67), post-exercise cardiac dysfunction (68), an increased incidence of arrhythmias (69), accelerated coronary artery calcifications (70), and an increased risk for cardiovascular morbidity and mortality at high amounts of exercise compared to light-to-moderate amounts of exercise (6,7). These observations among marathon runners, triathletes, cross-country skiers and cyclists raise the question of whether such athletes may experience potentially detrimental cardiac side effects from their exercise habits (71).

Exercise-induced, acute elevations in cardiac troponin T and I are observed in athletes participating in running races (15km / 21km / 42km) (72), triathlons (73), endurance cycling (74), ultra-endurance races (75), but also in individuals from the general population performing prolonged walking exercise (76). Post-exercise troponin concentrations are related to the covered distance (72), exercise intensity (77) and exceed the upper reference limit for an acute myocardial infarction in >50% of the athletic population (66). Although these findings suggest cardiac damage due to exercise performance, the kinetics of troponin release is different between patients and athletes. Athletes demonstrate modestly elevated peak troponin levels which normalize within 72 hours post-exercise in absence of any signs or symptoms of ischemia (78). In contrast, peak troponin concentrations can increase up to 50x the upper limit of normal and remain elevated for 4 to 10 days in acute myocardial infarction patients in conjunction with acute ECG changes and imaging

evidence of ischemia (79). It is therefore hypothesized that troponin elevations in athletes represent a physiological rather than a pathological phenomenon (80), potentially caused by troponin leaks from the cytosol of cardiomyocytes due to an exercise-induced increase in membrane permeability.

Small cardiac foci of late gadolinium enhancement (LGE) have been found during cardiac magnetic resonance imaging in some (67,81,82), but not all (83,84) studies of endurance athletes. These observations provide evidence of myocardial fibrosis, possibly increasing the risk of cardiac arrhythmia and mortality (85,86). The presence of myocardial fibrosis was observed in 12% to 50% of the athletes and was associated with longer endurance exercise participation, years of training and number of completed marathons (67,81,82). Fibrosis was frequently found where the right ventricle inserts into the septum, a location that is rarely observed in ischemic cardiac patients. Interestingly, comparable patterns are observed in hypertrophic cardiomyopathy patients (87). Similarly, faint LGE has been observed at the superior and inferior insertion points of the right and left ventricles of patients whose right ventricle was forced to produce systemic pressures after atrial redirection surgery for transposition of the great vessels (88). This suggest a non-ischemic etiology for the fibrosis found in athletes and that it is possibly due to the increase in mechanical stress on the right ventricle during exercise (89). Nevertheless, athletes with late gadolinium enhancement demonstrated a worse event free survival compared to those without imaging abnormalities (75% versus 99%, $p<0.001$) in one study (81).

Post-exercise decreases in left and right ventricular function are observed in some endurance athletes, with a larger decrement in the right *versus* left ventricle (75,90). The magnitude of the reduction in cardiac function is associated with longer exercise duration (67) and lower training status (91). This cardiac dysfunction is mild and typically recovers

within 48 hours after exercise cessation (92). Exercise-induced right ventricular dysfunction appears to be more pronounced in athletes with ventricular arrhythmias compared to healthy athletes (93). Whether athletes with a transient decline in cardiac function are at risk for future arrhythmias is currently unknown.

The association between physical activity patterns and incident atrial fibrillation is complicated. A greater leisure-time activity, greater walking distance, faster walking pace and higher cardiorespiratory fitness were associated with a graded risk reduction for atrial fibrillation in the Cardiovascular Health Study (N=5,446) and Henry Ford Exercise Testing (FIT) Project (N=64,561) (94,95). In contrast, a meta-analysis (N= 1550) reported a 5 fold increase in the relative risk for atrial fibrillation in athletes (OR 5.3, CI 3.6-7.9) compared to the general population (96). Also, a large Swedish study (N=52,755) confirmed these findings and observed a higher incidence of atrial fibrillation in participants completing ≥5 *versus* 1 *Vasaloppet* cross-country ski-races (HR 1.29, CI 1.04–1.61) and in those with faster finishing times (100–160% *versus* >240% of winning time; HR 1.20, CI 0.93–1.55). A potential explanation for these apparently contradictory findings is that the relationship between physical activity may be U-shaped with moderate amounts of exercise decreasing, but large volumes of exercise increasing atrial fibrillation risk (95,97).

The physically active lifestyle of athletes does not prevent the development of central and peripheral atherosclerosis (98). In fact, greater coronary artery calcification (CAC) scores have been found in German marathon runners (median 36, IQR 0-217) compared to controls (median 12, IQR 0-78) matched for age and Framingham risk score (70), but this difference disappeared when the authors corrected for age only (median 38, IQR 3-187). Alternatively, the elevated CAC scores may be the result of plaque stabilization, as a higher CAC density is protective for future cardiovascular outcomes (99). This hypothesis aligns with

epidemiological observations of reduced cardiovascular morbidity and mortality in athletes compared to sedentary controls (100).

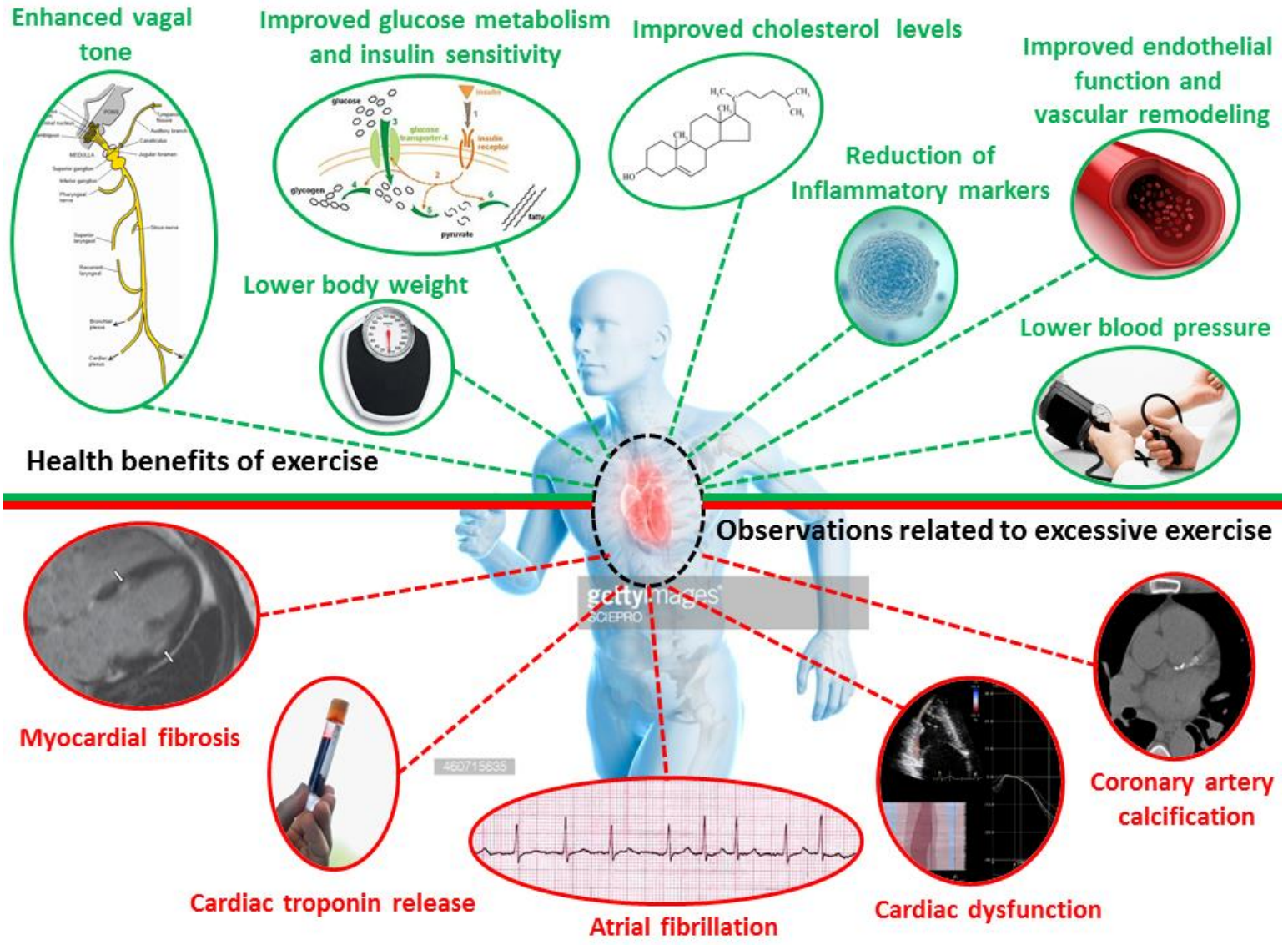
Two recent epidemiological studies reported a U-shaped relationship between aerobic exercise volumesand cardiovascular morbidity (7) and mortality (6) in the general population. A British study (N= 1,119,239) showed a lower incidence of cerebrovascular disease (RR 0.81, CI 0.78-0.84) and venous thromboembolism (RR 0.83, CI 0.79-0.87) in women performing 2-3 sessions/week of strenuous activities compared to inactive controls, but these health benefits disappeared in women performing daily strenuous activities (RR 0.96, CI 0.89-1.04 and RR 1.08, CI 0.99-1.17 respectively) (7). In contrast, daily activities regardless of the exercise intensity did reduce the incidence of cerebrovascular disease (RR 0.88, CI 0.86-0.91) and venous thromboembolism (RR 0.96, CI 0.93-1.00) compared to inactive controls. Also, any volume of (strenuous) exercise reduced the risk for incident coronary heart disease, even in women performing daily strenuous exercise (RR 0.89, CI 0.84-0.93) (7). An important caveat of this study was the higher smoking prevalence among daily strenuous exercisers (25.6%) compared all other exercise groups (13.7-15.5%). This may partially explain the absence of exercise-induced health benefits in the most active individuals. A Danish study including joggers (N=1,098) and non-joggers (N=3,950) reported similar findings for all-cause mortality (6). Arbitrarily classified 'light' joggers (HR 0.22, CI 0.10-0.47) had a lower mortality risk compared to non-joggers, whereas mortality rates in 'moderate' (HR 0.66, CI 0.32-1.38) and 'strenuous' joggers (HR 1.97, CI 0.48-8.14) were comparable to non-joggers (6). For any other classification of physical activity (quantity, frequency or pace), however, the most active group always demonstrated a lower mortality compared to non-joggers. Other important study limitations include the low number of subjects in the 'strenuous' jogger group and the fact that inclusion in the non-joggers' group

allowed participants to walk or bike up to 2 hours/week (101). Given the methodological limitations of these 2 studies, it is premature to conclude that high exercise volumes, compared to light-to-moderate volumes, could increase CVD risk.

The exercise-induced changes in cardiac structure and function are often related to the volume (late gadolinium enhancement, cardiac dysfunction and CAC) and intensity (troponin release and atrial fibrillation) of activities performed by athletes. For most observations, the long-term clinical implications are currently unknown, but it is unlikely that these are similar to risk classifications in CVD patient populations. For example, recreational marathon training has been shown to have a positive impact on several determinants of cardiovascular risk (102). Also, lifelong patterns of "committed" exercise (4 to 5 sessions/week) and "competitive" Masters level athletes prevents most of the age-related LV stiffening changes implicated in the pathophysiology of many cardiovascular disorders (103). Furthermore, leisure-time runners have lower all-cause (HR 0.70, CI 0.64–0.77) and cardiovascular mortality rates (HR 0.55, CI 0.46–0.65) compared to non-runners (33). These observations are not limited to amateur athletes, but include elite athletes, who were engaged in high volumes of vigorous exercise for many years, yet demonstrated a 3 to 6 year increased in life expectancy compared to controls from general (104-106) and military (107) populations. Mortality risk reductions were larger for older athletes and those who participated in multiple races (100). These findings suggest that athletes performing exercise volumes at the upper end of the physical activity spectrum do not demonstrate an increased risk for adverse cardiovascular outcomes on a population level.

Even though exercise and exercise training appears to benefit the majority, there may be individuals with genetic predisposition for cardiac disease in whom exercise training is not beneficial. Physically active individuals with genetic defects in the desmosomal

proteins associated with right ventricular cardiomyopathy presented earlier in life and had signs of more aggressive disease than less physically active individuals with similar genetic mutations (108). Whether similar patterns exist for other genetic mutations is worthy of investigation.


Enhanced vagal tone
Improved glucose metabolism and insulin sensitivity
Improved cholesterol levels
Improved endothelial function and vascular remodeling
Reduction of Inflammatory markers
Lower body weight
Lower blood pressure
Health benefits of exercise
Observations related to excessive exercise
Myocardial fibrosis
Cardiac troponin release
Atrial fibrillation
Cardiac dysfunction
Coronary artery calcification

Central illustration: *E*xercise training reduces cardiovascular disease morbidity and mortality via several mechanisms (green circles), with a graded risk reduction with increasing exercise volumes. Regular physical activity is therefore recommended for primary and secondary prevention purposes. Some studies reported unexpected cardiovascular outcomes (red circles) in athletes, which may relate to (long-term) exposure of excessive exercise volumes. Although future studies are warranted to investigate the clinical meaning of these phenomena, life-long endurance athletes live longer compared to non-athletes. The benefits of exercise training therefore outweigh the (potential) risks.

5.0 Conclusions

This review demonstrates that even small amounts of physical activity including activities such as standing are associated with lower CVD risk. Exercise volumes of 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic exercise, such as recommended in the 2008 Physical Activity Guidelines Advisory Committee Report, further reduce CVD mortality. The possibility that too much exercise training could produce deleterious cardiac effects including myocardial fibrosis, coronary calcification, and atrial fibrillation is interesting and worthy of scientific investigation, but overall the results, even for very active, life-long endurance athletes, is that the benefits of exercise training outweigh the risks. There may also be small subsets of the population with genetic predispositions to cardiac disease for whom vigorous exercise is not beneficial and may even be deleterious, though this represents a very small subset of patients. Moreover, the issue for most developed countries and the majority of their citizens is not concern about too much exercise, but rather the absence of any exercise among most of the population and among patients with CVD. For example, only 62% of 58,269 post-infarction patients were referred to cardiac rehabilitation at hospital discharge (109), whereas only 23% attended ≥1 cardiac rehabilitation session and only 5.4% completed ≥36 sessions. This may reflect in part, a lack of clinician enthusiasm for such programs despite the evidence that cardiac rehabilitation saves lives. The available evidence should prompt clinicians to recommend strongly low and moderate exercise training for the majority of our patients. Equally important are initiatives to promote population health at large through physical activity across the life span, as it modulates behavior from childhood into adult life.

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