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THE PRESENT AND FUTURE

COUNCIL PERSPECTIVES

Exercise at the Extremes

The Amount of Exercise to Reduce Cardiovascular Events

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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. (J Am Coll Cardiol 2016;67:316–29)
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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 U.S. adults (**Table 1**) (3), because this exercise volume provides significant health improvements for most people much of the time. However, only one-half of Americans meet these guidelines (4). In contrast, 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 (5,6). 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 (7–10). 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 (11). This document will review the published data on the volume and intensity of aerobic exercise required for favorable

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Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

cardiovascular health and will also address the question as to whether or not there is a volume that increases CVD risk.

EXERCISE IN PRIMARY PREVENTION

GENERAL BENEFITS OF EXERCISE. The health benefits of exercise have been recognized since the epidemiological studies of Morris et al. (13), who in the 1950s reported lower rates of coronary heart disease among the conductors of London's double-decker buses compared with the drivers. Morris et al. (13) also reported a lower incidence of coronary heart disease among English postmen compared with telephone operators working at the same company. 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 (14–16), 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 crossover 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. (17) 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 (18), a relationship also lacking a randomized, controlled clinical trial. They demonstrated that the relationship between physical activity and CVD was strong, was consistent among studies, had 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 (17). They concluded that increasing physical activity was causally related to lower rates of CVD despite the absence of the classical clinical trial.

TABLE 1 Examples of Moderate- and Vigorous-Intensity Activities to Achieve 2008 Exercise Guideline Recommendations

Moderate-Intensity Aerobic Activities >150 min/week	Vigorous-Intensity Aerobic Activities >75 min/week
Brisk walking (>3 miles/h)	Uphill walking or race walking
Bicycling (<10 miles/h)	Bicycling (>10 miles/h)
Water aerobics	Running or jogging
Tennis (doubles)	Tennis (singles)
Ballroom dancing	Aerobic dancing
General gardening	Heavy gardening (digging/hoeing)

From the Centers for Disease Control and Prevention guidelines (12).

The CVD benefits of exercise are likely mediated via multiple mechanisms. Regular exercise training improves the CVD risk profile by reducing triglycerides and increasing high-density lipoprotein cholesterol (19), lowering blood pressure (20), improving glucose metabolism and insulin sensitivity (21), reducing body weight, and reducing inflammatory markers (22). These risk factor improvements explain 59% of the reduction in CVD (23). The remaining 41% may result from improved endothelial function (24), enhanced vagal tone producing lower heart rates (25), vascular remodeling including larger vessel diameters, and an enhanced nitric oxide bioavailability.

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**) (26). 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, although 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 h/day is associated with a 10% reduction of all-cause mortality (hazard ratio [HR]: 0.90; 95% CI: 0.85 to 0.95) compared with standing <2 h/day (27). Increased standing time was associated with larger risk reductions, with the lowest mortality in individuals standing ≥8 h/day (HR: 0.76; 95% CI: 0.69 to 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 age ≥45 years and the results were independent of health status and were not altered by sex, age, body mass index, other physical activity, and sitting time (27). Similar reductions in all-cause mortality with standing were observed prospectively in 16,586 Canadians (28), 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; 95% CI: 0.68 to 0.99 and HR: 0.68; 95% CI: 0.50 to 0.92) (28). This dose-response relationship between standing and CVD mortality informs on the lower end

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcification

CVD = cardiovascular disease

HIIT = high-intensity interval training

IQR = interquartile range

MET = metabolic equivalent of task score

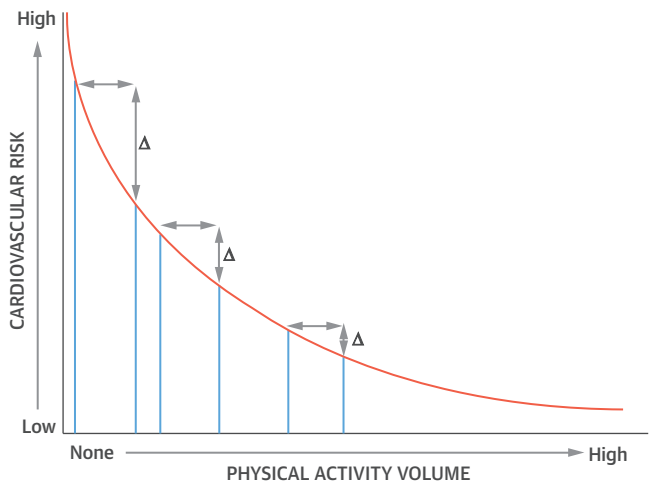
MI = myocardial infarction

MICT = moderate intensity continuous training

QOL = quality of life

SCD = sudden cardiac deaths

FIGURE 1 The Curvilinear Relationship Between Physical Activity and Cardiovascular Risk

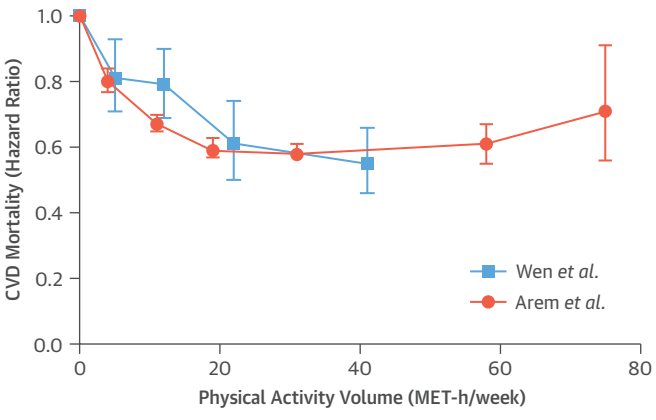


A similar increase in physical activity yields different risk reductions across the activity spectrum. Physical inactivity is associated with the highest risk, whereas high aerobic exercise volumes are associated with the lowest risk (26).

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 (29).

FIGURE 2 The Dose-Response Curve of Physical Activity and Cardiovascular Mortality



On the basis of data from the studies of Wen et al. (35) **(blue squares)** and Arem et al. (36) **(orange circles)**. 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. (36). The maximal risk reduction for cardiovascular mortality was found at an exercise volume of 41 MET-h/week. CVD = cardiovascular disease; MET = metabolic equivalent of task score.

Importantly, the detrimental effects of sitting appear to be independent from the benefits of physical activity (30). Recent studies demonstrate that breaking up sitting time improves cardiovascular health (31) and glucose homeostasis (32), and replacement of sitting time effectively reduces all-cause mortality (33). 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 (34-36) 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; 95% CI: 0.31 to 0.66) and all-cause mortality (HR: 0.70; 95% CI: 0.58 to 0.85) compared with nonrunners (34). Similarly, Taiwanese engaging in moderate-intensity exercise 92 min/week, or 61% of the recommended volume, experienced a reduction in CVD mortality (HR: 0.81; 95% CI: 0.71 to 0.93) and all-cause mortality (HR: 0.86; 95% CI: 0.81 to 0.91) compared with their inactive peers (35). 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; 95% CI: 0.77 to 0.84) and all-cause mortality (HR: 0.80; 95% CI: 0.78 to 0.82) compared with inactive control subjects (36). These data emphasize that even low exercise volumes can effectively reduce CVD mortality, a message that clinicians should communicate to stimulate vulnerable populations to become physically active.

The volume of aerobic exercise to improve CVD outcomes maximally is difficult to determine. 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 (37) multiplied by an assessment of the frequency (sessions/week) and duration (h/week) to calculate the exercise volume in MET-h/week. We combined data from Taiwanese (35), American, and European population studies (36) 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× 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; 95% CI: 0.46 to 0.66) compared with inactive control subjects.

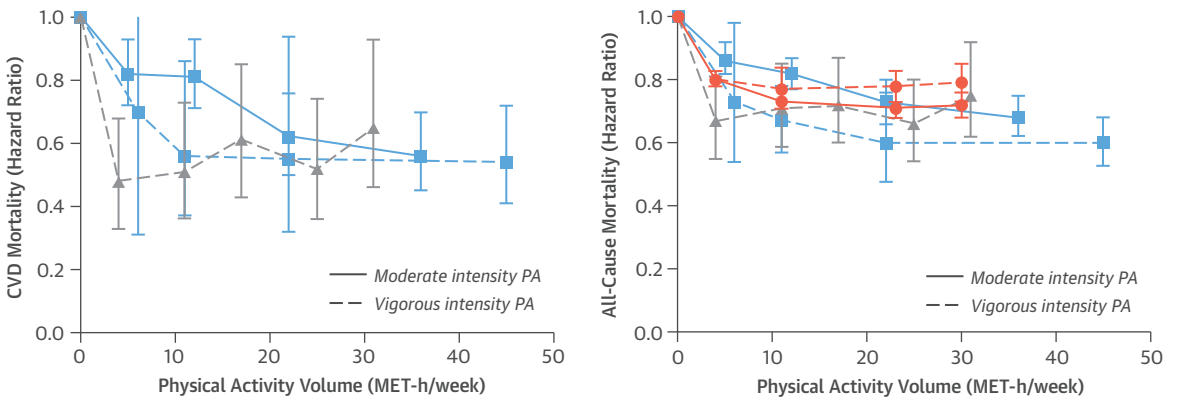
Only 3.5% of individuals included in the meta-analysis mentioned exceed the exercise volume that was associated with maximal health benefits (36). These individuals experienced reductions in CVD mortality comparable to the "maximal benefit" group (HR: 0.61; 95% CI: 0.55 to 0.67; and HR: 0.71; 95% CI: 0.56 to 0.91 for subjects performing 40 to 75 MET-h/week and >75 MET-h/week, respectively) (36), 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 appears to be safe because there is no evidence for adverse CVD outcomes among these individuals.

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 with moderate-intensity, continuous training (38). Higher fitness levels are associated with a reduction in CVD (39) and all-cause mortality (40) 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 with individuals performing only moderate-intensity exercise (HR: 0.91; 95% CI: 0.84 to 0.98 and HR: 0.87; 95% CI: 0.81 to 0.93, respectively) after adjusting for total volume of moderate- to vigorous-intensity activities (41). 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 (42).

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 an excess of 11 MET-h/week (34,35). Similar patterns exist for all-cause mortality, although the differences between moderate and vigorous intensity activity were less pronounced (34–36) (**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 (43–45). A total of 122 sudden cardiac deaths (SCDs), 23 (18.9%) of which were exercise related, occurred in a study of 21,481 male physicians (45). The absolute

FIGURE 3 The Dose-Response Curve of Moderate- and Vigorous-Intensity Physical Activity and Cardiovascular and All-Cause Mortality



The dose-response curve of moderate-intensity **(solid lines)** and vigorous-intensity **(dashed lines)** physical activity and cardiovascular **(left)** and all-cause mortality **(right)** based on data from the studies of Wen et al. (35) **(blue squares)**, Lee et al. (34) **(gray triangles)**, and Arem et al. (36) **(orange circles)**. 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. (36). 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. PA = physical activity; other abbreviations as in **Figure 2**.

risk for a vigorous exercise-related SCD was low at 1 per 1.42 million hours, but 16.9% higher (95% 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 an RR of 74.1 for those exercising vigorously <1 session/week (95% CI: 22.0 to 249) versus an RR of 18.9 for those exercising vigorously 1 to 4 sessions/week (95% CI: 10.2 to 35.1) versus an RR of 10.9 for those exercising vigorously ≥5 sessions/week (95% CI: 4.5 to 26.2) (45). The pattern is similar for the association between vigorous exertion and acute myocardial infarction (MI) in the general population (44). Among 1,228 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 with sedentary individuals (no sessions/week, RR: 107) (44). 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 with physical inactivity.

EXERCISE IN SECONDARY PREVENTION

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**) (46–50). The recommend exercise volume is generally similar to that for healthy adults: 30 to 60 min/day of moderate-intensity aerobic activities. Exercise can be performed as a part of a clinical rehabilitation program 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 with aerobic exercise alone (51). 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 (51). Increased QOL may occur because the increases in exercise capacity and strength increase self-confidence and independence after a CVD event.

CARDIAC REHABILITATION. Patients with stable angina pectoris, systolic heart failure, MI, 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 (52). The goal is to reduce CVD risk via pharmacotherapy, improved health behavior, and a physically active life-style.

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 (53) demonstrated that cardiac rehabilitation reduced all-cause (RR: 0.87; 95% CI: 0.75 to 0.99) and CVD mortality (RR: 0.74; 95% CI: 0.63 to 0.87) after >1 year of follow-up. Furthermore, a decrease in hospital admissions was found in the cardiac rehabilitation *versus* the standard care group within 1 year of follow-up (RR: 0.69; 95% CI: 0.51 to 0.93). A meta-analysis including 6,111 post-MI patients from 34 randomized controlled clinical trials showed similar results, with exercise-based rehabilitation demonstrating a lowered risk for all-cause mortality (odds ratio [OR]: 0.74; 95% CI: 0.58 to 0.95), CVD mortality (OR: 0.61; 95% CI: 0.40 to 0.91), cardiac mortality (OR: 0.64; 95% CI: 0.46 to 0.88), and reinfarction (OR: 0.54; 95% CI: 0.38 to 0.76) (54).

A Cochrane review of 33 randomized clinical trials including 4,740 patients with predominantly systolic heart failure (55) demonstrated that cardiac rehabilitation and exercise training reduced all-cause (RR: 0.75; 95% CI: 0.62 to 0.92) and heart failure-specific (RR: 0.61; 95% CI: 0.46 to 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; 95% CI: 0.69 to 1.27), but trended toward significance in follow-up >1 year (RR: 0.88; 95% CI: 0.75 to 1.02) (55).

TABLE 2 Physical Activity and/or Exercise Recommendations for Cardiac Patient Populations

Recommendations for Cardiac Patient Populations (Ref. #)	Class of Recommendation	Level of Evidence
Congenital heart disease (46)		
Exercise prescription, guidelines for exercise, and athletic participation for patients with congenital heart disease should reflect the published recommendations of the 36th Bethesda Conference report.	I	C
Heart failure (47)		
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-segment elevation acute coronary syndromes (48)		
All eligible patients with non–ST-segment 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 (e.g., 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
STEMI (49)		
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 (50)		
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 min 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 life-style 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

STEMI = ST-segment elevation myocardial infarction.

HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) 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 (interquartile range [IQR]: -1.0 to 2.5 ml/kg/min), 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 nonexercise training usual care group (HR: 0.87; 95% CI: 0.75 to 1.00) (56). After correction for highly prognostic baseline factors and heart failure etiology, these findings became statistically significant (HR: 0.85; 95% CI: 0.74 to 0.99). Patients receiving exercise training also reported an earlier and larger improvement in self-reported health status, which persisted over time (57).

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× weekly for 30 to 40 min/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× greater than their risk at rest (58). The risk of a cardiac event during contemporary cardiac rehabilitation is low: estimated at only 1 cardiac arrest per 116,906 patient-hours of participation and 1 fatality per 752,365 patient-hours (59). 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 volume on 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 (60). Heart failure patients performing exercise ≥5 MET-h/week had a higher event-free survival compared with those performing lower volumes of exercise (i.e., <1, 1 to 3, or 3 to 5 MET-h/week). However, after correction for peak VO_2 values, a J-shaped curve appeared, with the largest risk reductions in patients exercising 3 to 7 MET-h/week and less benefit for patients exercising ≥7 MET-h/week (60).

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. (10) recorded the baseline exercise habits and health outcomes of 2,377 subjects who were self-identified as heart attack survivors at baseline. A total of 526 died over an average follow-up of 10.4 years; 71.5% died 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 to 50 MET-h/week compared with 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 was not different from the least active group (**Central Illustration**).

These data from Williams et al. (10) show an attenuation of mortality risk reductions in patients with the highest levels of exercise. Studies by both Wannamethee et al. (61) and Mons et al. (9) also show an apparent reduction in the benefit of exercise in the most active subjects. Among 772 British patients with coronary heart disease (61), lightly and moderately active patients had a significantly lower all-cause and CVD-related mortality risk compared with inactive patients, whereas moderately to vigorously active patients did not (**Central Illustration**). Similarly, Mons et al. (9) found that among 1,038 German coronary heart disease patients, patients exercising 2 to 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 (**Central Illustration**). In contrast, the examination by Moholdt et al. (62) of 3,504 Norwegian patients with coronary heart disease observed no attenuated mortality risk reduction in the most active group (**Central Illustration**). These current studies are limited by their observational nature, their 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.

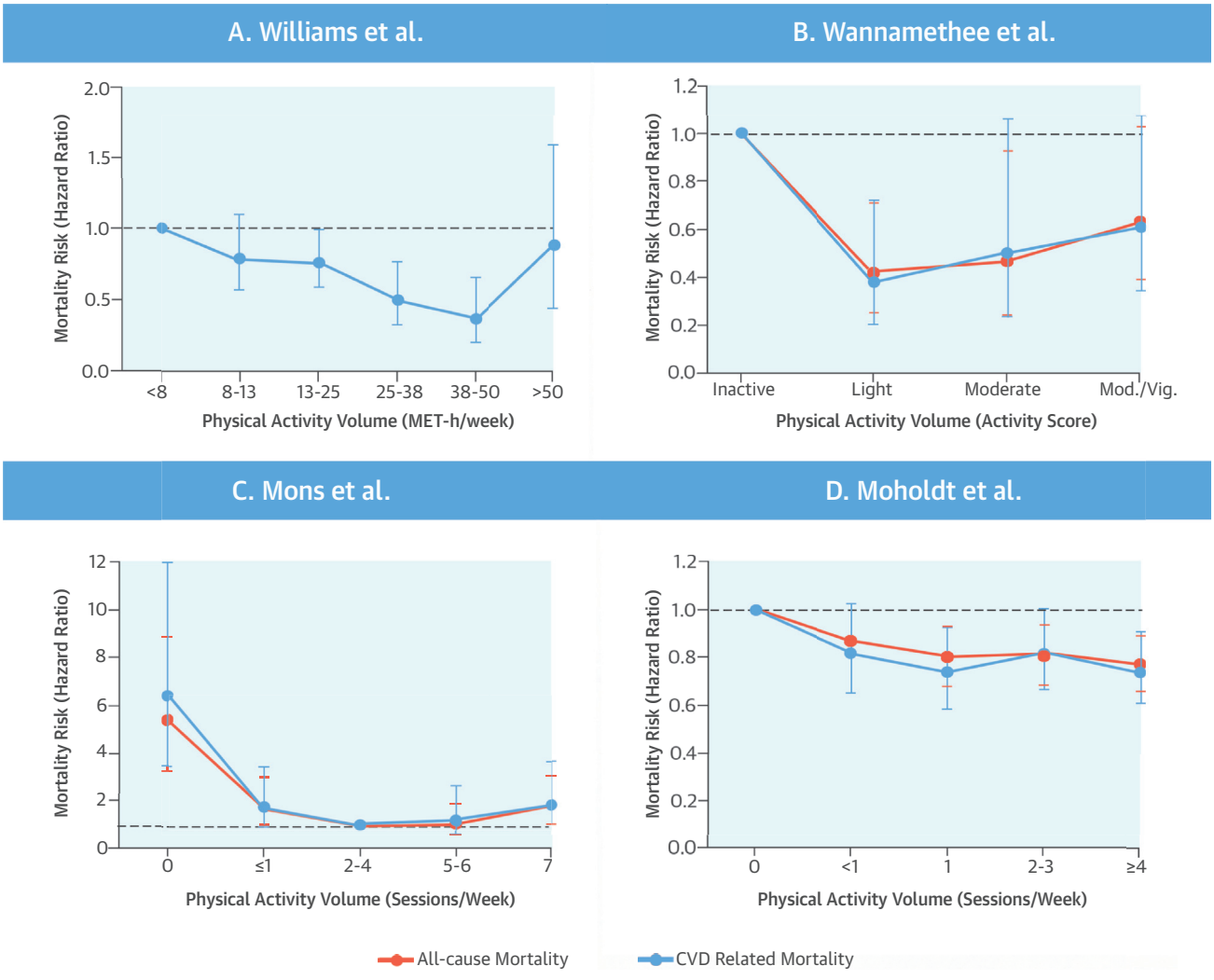
Despite these concerns about the volume and intensity of exercise in CVD patients, several studies have explored strategies to optimize the effects of cardiac rehabilitation using high-intensity interval training (HIIT), modeled after athletic training programs. HIIT was introduced into cardiac rehabilitation in 2007 and typically consists of a 10-min warm-up at 60% to 70% of peak heart rate, followed by 4 4-min intervals at 90% to 95% of peak heart rate separated by 3-min active pauses at 50% to 70% of peak heart rate (63). The exercise session is ended by a 3-min cool down at 50% to 70% of peak heart rate (**Figure 4**).

Heart failure patients receiving HIIT demonstrated a 46% improvement in cardiorespiratory fitness (VO_{2peak}) compared with 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% to 75% of peak heart rate (**Figure 4**) (63).

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; 95% CI: 0.84 to 2.23) compared with MICT (64). Similarly, a meta-analysis comparing changes in fitness in cardiac rehabilitation trials for heart failure that included 5,877 patients found larger improvements in VO_{2peak} for training programs using higher exercise intensities (65). 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 personnel. 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 (66). These data suggest a higher risk for adverse CVD outcomes with HIIT, but there were only 1 fatal cardiac arrest

CENTRAL ILLUSTRATION **The Amount of Exercise to Reduce Cardiovascular Events in Cardiac Patient Populations**



Eijsvogels, T.M.H. et al. J Am Coll Cardiol. 2016; 67(3):316–29.

The dose-response curve of physical activity and all-cause **(red lines)** and cardiovascular mortality **(blue lines)** among cardiac patient populations. Data were extracted from the studies of **(A)** Williams et al. (10), **(B)** Wannamethee et al. (61), **(C)** Mons et al. (9), and **(D)** Moholdt et al. (62). CVD = cardiovascular disease; MET = metabolic equivalent of task score; Mod./Vig. = moderate to vigorous.

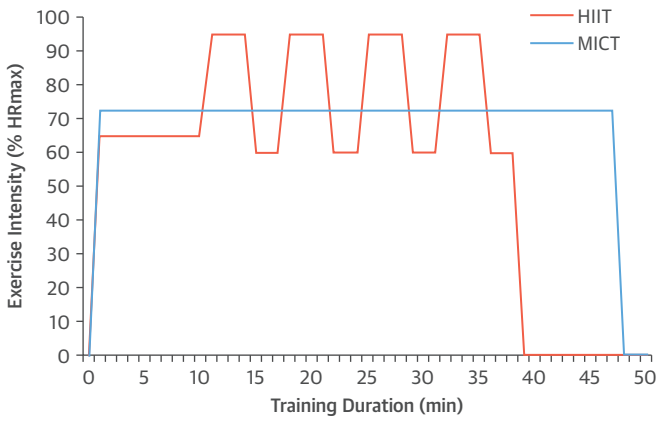
and 2 nonfatal cardiac arrests with MICT and HIIT, respectively, so there were too few events and insufficient power to compare risk.

Taken together, referral to an exercise rehabilitation program is recommended for cardiac patients, because 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 SCD 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 (46–50) should therefore be recommended for cardiac patients by their clinicians to achieve maximal cardiovascular benefits.

THE CONTROVERSY OF EXCESSIVE EXERCISE

The amount of habitual exercise training required to be a successful endurance athlete is markedly higher

FIGURE 4 Example of a HIIT Protocol Versus an MICT Protocol in Cardiac Rehabilitation



Both exercise protocols are isocaloric (63). HIIT = high-intensity interval training; HRmax = maximal heart rate; MICT = moderate-intensity continuous training.

than that required for cardiovascular health. Multiple studies have reported unexpected, potentially adverse cardiovascular outcomes in athletes. For example, some athletes demonstrate exercise-induced elevations in cardiac troponin levels (67), evidence of myocardial fibrosis (68), post-exercise cardiac dysfunction (69), an increased incidence of arrhythmias (70), accelerated coronary artery calcifications (71), and an increased risk for cardiovascular morbidity and mortality at high amounts of exercise compared with light to moderate amounts of exercise (7,8). 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 (72).

Exercise-induced, acute elevations in cardiac troponin T and I are observed in athletes participating in running races (15, 21, or 42 km) (73), triathlons (74), endurance cycling (75), and ultra-endurance races (76), but also in individuals from the general population performing prolonged walking exercise (77). Post-exercise troponin concentrations are related to the covered distance (73) and exercise intensity (78), and exceed the upper reference limit for an acute MI in >50% of the athletic population (67). Although these findings suggest cardiac damage due to exercise performance, the kinetics of troponin release are different between patients and athletes. Athletes demonstrate modestly elevated peak troponin levels that normalize within 72 h post-exercise in absence of any signs or symptoms of ischemia (79). In contrast, peak troponin concentrations can increase up to 50× the upper limit of normal and remain elevated for 4 to 10 days in acute MI patients in conjunction with acute electrocardiogram changes and imaging evidence of ischemia (80). It is therefore hypothesized that troponin elevations in athletes represent a physiological rather than a pathological phenomenon (81), 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 have been found during cardiac magnetic resonance imaging in some (68,82,83), but not all (84,85) studies of endurance athletes. These observations provide evidence of myocardial fibrosis, possibly increasing the risk of cardiac arrhythmia and mortality (86,87). The presence of myocardial fibrosis was observed in 12% to 50% of the athletes and was associated with longer endurance exercise participation and higher years of training and number of completed marathons (68,82,83). 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 (88). Similarly, faint late gadolinium enhancement 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 (89). This suggests a nonischemic 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 (90). Nevertheless, athletes with late gadolinium enhancement demonstrated a worse event-free survival compared with those without imaging abnormalities (75% vs. 99%; $p < 0.001$) in 1 study (82).

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 (76,91). The magnitude of the reduction in cardiac function is associated with longer exercise duration (68) and lower training status (92). This cardiac dysfunction is mild and typically recovers within 48 h after exercise cessation (93). Exercise-induced right ventricular dysfunction appears to be more pronounced in athletes with ventricular arrhythmias compared with healthy athletes (94). 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. More 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) (95,96). In contrast, a meta-analysis (N = 1,550) reported a 5-fold increase in the relative risk for atrial fibrillation in athletes (OR: 5.3; 95% CI: 3.6 to 7.9) compared with the general population (97). 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; 95% CI: 1.04 to 1.61) and in those with faster finishing times (100% to 160% vs. >240% of winning time; HR: 1.20; 95% CI: 0.93 to 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 (96,98).

The physically active lifestyle of athletes does not prevent the development of central and peripheral atherosclerosis (99). In fact, greater coronary artery calcification (CAC) scores have been found in German marathon runners (median 36; IQR: 0 to 217) compared with control subjects (median 12; IQR: 0 to 78) matched for age and Framingham risk score (71), but this difference disappeared when the authors corrected for age only (median 38; IQR: 3 to 187). Alternatively, the elevated CAC scores may be the result of plaque stabilization, as a higher CAC density is protective for future cardiovascular outcomes (100). This hypothesis aligns with epidemiological observations of reduced cardiovascular morbidity and mortality in athletes compared with sedentary control subjects (101).

Two recent epidemiological studies reported a U-shaped relationship between aerobic exercise volumes and cardiovascular morbidity (8) and mortality (7) in the general population. A British study (N = 1,119,239) showed a lower incidence of cerebrovascular disease (RR: 0.81; 95% CI: 0.78 to 0.84) and venous thromboembolism (RR: 0.83; 95% CI: 0.79 to 0.87) in women performing 2 to 3 sessions/week of strenuous activities compared with inactive control subjects, but these health benefits disappeared in women performing daily strenuous activities (RR: 0.96; 95% CI: 0.89 to 1.04; and RR: 1.08; 95% CI: 0.99 to 1.17, respectively) (8). In contrast, daily activities regardless of the exercise intensity did reduce the incidence of cerebrovascular disease (RR: 0.88; 95% CI: 0.86 to 0.91) and venous thromboembolism (RR: 0.96; 95% CI: 0.93 to 1.00) compared with inactive control subjects. Also, any volume of (strenuous) exercise reduced the risk for incident coronary heart disease, even in women performing daily strenuous exercise (RR: 0.89; 95% CI: 0.84 to 0.93) (8). An important caveat of this study was the higher smoking prevalence among daily strenuous exercisers (25.6%) compared with all other exercise groups (13.7% to 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 nonjoggers (n = 3,950) reported similar findings for all-cause mortality (7). Arbitrarily classified "light" joggers (HR: 0.22; 95% CI: 0.10 to 0.47) had a lower mortality risk compared with nonjoggers, whereas mortality rates in "moderate" (HR: 0.66; 95% CI: 0.32 to 1.38) and "strenuous" joggers (HR: 1.97; 95% CI: 0.48 to 8.14) were comparable to nonjoggers (7). For any other classification of physical activity (quantity, frequency, or pace), however, the most active group always demonstrated a lower mortality compared with nonjoggers. Other important study limitations include the low number of subjects in the strenuous jogger group and the fact that inclusion in the nonjoggers group allowed participants to walk or bike up to 2 h/week (102). Given the methodological limitations of these 2 studies, it is premature to conclude that high exercise volumes, compared with 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 effect on several determinants of cardiovascular risk (103). Also, lifelong patterns of "committed" exercise (4 to 5 sessions/week) and "competitive" Masters-level athletes prevents most of the age-related left ventricular stiffening changes implicated in the pathophysiology of many cardiovascular disorders (104). Furthermore, leisure-time runners have lower all-cause (HR: 0.70; 95% CI: 0.64 to 0.77) and cardiovascular mortality rates (HR: 0.55; 95% CI: 0.46 to 0.65) compared with nonrunners (34). 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 increase in life expectancy compared with control subjects from general (105–107) and military (108) populations. Mortality risk reductions were larger for older athletes and those who participated in multiple races (101). 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 of people, 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 (109). Whether similar patterns exist for other genetic mutations is worthy of investigation.

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; however, 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, although 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 (110), 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 strongly recommend 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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REFERENCES

1. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation 2003;107:3109–16.

2. Fletcher GF, Balady G, Blair SN, et al. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation 1996;94:857–62.

3. Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report*, 2008. Washington DC, U.S. Department of Health and Human Services.

4. Centers for Disease Control and Prevention. Nutrition, physical activity and obesity: data, trends and maps. Available at: http://nccd.cdc.gov/NPAO_DTM. Accessed September 30, 2015.

5. Knechtle B, Knechtle P, Lepers R. Participation and performance trends in ultra-triathlons from 1985 to 2009. Scand J Med Sci Sports 2011;21:e82–90.

6. Running USA. Statistics. Available at: http://www.runningusa.org/statistics. Accessed August 5, 2015.

7. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality: the Copenhagen City Heart Study. J Am Coll Cardiol 2015;65:411–9.

8. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ, for the Million Women Study Collaborators. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. Circulation 2015;131:721–9.

9. Mons U, Hahmann H, Brenner H. A reverse J-shaped association of leisure time physical activity with prognosis in patients with stable coronary heart disease: evidence from a large cohort with repeated measurements. Heart 2014;100:1043–9.

10. Williams PT, Thompson PD. Increased cardiovascular disease mortality associated with excessive exercise in heart attack survivors. Mayo Clin Proc 2014;89:1187–94.

11. Eijsvogels TM, Thompson PD. Exercise is Medicine: at any dose? JAMA 2015;314:1915–6.

12. Centers for Disease Control and Prevention. General physical activities defined by level of intensity. Available at: http://www.cdc.gov/nccdphp/dnpa/physical/pdf/PA_Intensity_table_2_1.pdf. Accessed September 18, 2015.

13. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. Lancet 1953;265:1111–20, concl.

14. Paffenbarger RS Jr., Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol 1978;108:161–75.

15. Paffenbarger RS Jr., Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. N Engl J Med 1986;314:605–13.

16. Paffenbarger RS Jr., Laughlin ME, Gima AS, Black RA. Work activity of longshoremen as related to death from coronary heart disease and stroke. N Engl J Med 1970;282:1109–14.

17. Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. Annu Rev Public Health 1987;8:253–87.

18. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington D.C.: U.S. Department of Health, Education, And Welfare, 1964: 1–386. Available at: http://profiles.nlm.nih.gov/NN/B/B/M/Q/. Accessed August 14, 2015.

19. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. Sports Med 2014;44: 211–21.

20. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med 2002;136:493–503.

21. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev 2006:CD002968.

22. Szostak J, Laurant P. The forgotten face of regular physical exercise: a 'natural' anti-atherogenic activity. Clin Sci (Lond) 2011;121: 91–106.

23. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. Circulation 2007;116:2110–8.

24. Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. J Physiol 2009;587:5551–8.

25. Beere PA, Glagov S, Zarins CK. Experimental atherosclerosis at the carotid bifurcation of the cynomolgus monkey. Localization, compensatory enlargement, and the sparing effect of lowered heart rate. Arterioscler Thromb 1992;12:1245–53.

26. Powell KE, Paluch AE, Blair SN. Physical activity for health: what kind? How much? How intense? On top of what? Annu Rev Public Health 2011;32:349–65.

27. van der Ploeg HP, Chey T, Ding D, Chau JY, Stamatakis E, Bauman AE. Standing time and all-cause mortality in a large cohort of Australian adults. Prev Med 2014;69:187–91.

28. Katzmarzyk PT. Standing and mortality in a prospective cohort of Canadian adults. Med Sci Sports Exerc 2014;46:940–6.

29. van der Ploeg HP, Chey T, Korda RJ, Banks E, Bauman A. Sitting time and all-cause mortality risk in 222 497 Australian adults. Arch Intern Med 2012;172:494–500.

30. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med 2015;162:123–32.

31. Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 2008;31:661–6.

32. Dunstan DW, Kingwell BA, Larsen R, et al. Breaking up prolonged sitting reduces postprandial glucose and insulin responses. Diabetes Care 2012;35:976–83.

33. Matthews CE, Moore SC, Sampson J, et al. Mortality benefits for replacing sitting time with different physical activities. Med Sci Sports Exerc 2015;47:1833–40.

34. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. J Am Coll Cardiol 2014;64:472–81.

35. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet 2011;378:1244–53.

36. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med 2015;175:959–67.

37. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575–81.

38. Milanovic Z, Sporis G, Weston M. Effectiveness of high-intensity interval training (HIT) and continuous endurance training for VO2max improvements: a systematic review and meta-analysis of controlled trials. Sports Med 2015;45: 1469–81.

39. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. Circulation 2011;124:2483–90.

40. Feldman DI, Al-Mallah MH, Keteyian SJ, et al. No evidence of an upper threshold for mortality benefit at high levels of cardiorespiratory fitness. J Am Coll Cardiol 2015;65:629–30.

41. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of moderate to vigorous physical activity on all-cause mortality in middle-aged and older australians. JAMA Intern Med 2015;175:970–7.

42. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. Am J Cardiol 2006; 97:141–7.

43. Kim JH, Malhotra R, Chiampas G, et al. Cardiac arrest during long-distance running races. N Engl J Med 2012;366:130–40.

44. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE, for the Determinants of Myocardial Infarction Onset Study Investigators. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. N Engl J Med 1993;329:1677–83.

45. Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. N Engl J Med 2000;343:1355–61.

46. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). J Am Coll Cardiol 2008;52:e143–263.

47. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64:e1–76.

48. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64: e1391–228.

49. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

50. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44–164.

51. Marzolini S, Oh PI, Brooks D. Effect of combined aerobic and resistance training versus aerobic training alone in individuals with coronary artery disease: a meta-analysis. Eur J Prev Cardiol 2012;19:81–94.

52. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation 2007;115:2675–82.

53. Heran BS, Chen JM, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev 2011: CD001800.

54. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Am Heart J 2011;162:571–84.e2.

55. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. Cochrane Database Syst Rev 2014;4:CD003331.

56. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

57. Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1451–9.

58. Cobb LA, Weaver WD. Exercise: a risk for sudden death in patients with coronary heart disease. J Am Coll Cardiol 1986;7:215–9.

59. Thompson PD, Franklin BA, Balady GJ, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation 2007;115:2358–68.

60. Keteyian SJ, Leifer ES, Houston-Miller N, et al. Relation between volume of exercise and clinical outcomes in patients with heart failure. J Am Coll Cardiol 2012;60:1899–905.

61. Wannamethee SG, Shaper AG, Walker M. Physical activity and mortality in older men with diagnosed coronary heart disease. Circulation 2000;102:1358–63.

62. Moholdt T, Wisloff U, Nilsen TI, Slordahl SA. Physical activity and mortality in men and women with coronary heart disease: a prospective population-based cohort study in Norway (the HUNT study). Eur J Cardiovasc Prev Rehabil 2008; 15:639–45.

63. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086–94.

64. Elliott AD, Rajopadhyaya K, Bentley DJ, et al. Interval training versus continuous exercise in patients with coronary artery disease: a meta-analysis. Heart Lung Circ 2015;24:149–57.

65. Ismail H, McFarlane JR, Nojoumian AH, et al. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. J Am Coll Cardiol HF 2013;1:514–22.

66. Rognmo O, Moholdt T, Bakken H, et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. Circulation 2012;126:1436–40.

67. Shave R, Baggish A, George K, et al. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. J Am Coll Cardiol 2010;56:169–76.

68. La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. Eur Heart J 2012;33:998–1006.

69. Oxborough D, Birch K, Shave R, George K. "Exercise-induced cardiac fatigue"—a review of the echocardiographic literature. Echocardiography 2010;27:1130–40.

70. Andersen K, Farahmand B, Ahlbom A, et al. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. Eur Heart J 2013; 34:3624–31.

71. Mohlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events: prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. Eur Heart J 2008;29:1903–10.

72. Eijsvogels TMH, Fernandez AB, Thompson PD. Are there deleterious cardiac effects of acute and chronic endurance exercise? Physiol Rev 2016;96: 99–125.

73. Mingels AM, Jacobs LH, Kleijnen VW, et al. Cardiac troponin T elevations, using highly sensitive assay, in recreational running depend on running distance. Clin Res Cardiol 2010;99:385–91.

74. Tulloh L, Robinson D, Patel A, et al. Raised troponin T and echocardiographic abnormalities after prolonged strenuous exercise—the Australian Ironman Triathlon. Br J Sports Med 2006;40: 605–9.

75. Neumayr G, Pfister R, Mitterbauer G, et al. Effect of the "Race Across The Alps" in elite cyclists on plasma cardiac troponins I and T. Am J Cardiol 2002;89:484–6.

76. La Gerche A, Connelly KA, Mooney DJ, et al. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. Heart 2008;94:860–6.

77. Eijsvogels T, George K, Shave R, et al. Effect of prolonged walking on cardiac troponin levels. Am J Cardiol 2010;105:267–72.

78. Eijsvogels TM, Hoogerwerf MD, Oudegeest-Sander MH, et al. The impact of exercise intensity on cardiac troponin I release. Int J Cardiol 2014; 171:e3–4.

79. Scherr J, Braun S, Schuster T, et al. 72-h kinetics of high-sensitive troponin T and inflammatory markers after marathon. Med Sci Sports Exerc 2011;43:1819–27.

80. Katus HA, Remppis A, Scheffold T, et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. Am J Cardiol 1991;67:1360–7.

81. Eijsvogels TM, Hoogerwerf MD, Maessen MF, et al. Predictors of cardiac troponin release after a marathon. J Sci Med Sport 2015;18:88–92.

82. Breuckmann F, Mohlenkamp S, Nassenstein K, et al. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. Radiology 2009;251:50–7.

83. Wilson M, O'Hanlon R, Prasad S, et al. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. J Appl Physiol 2011;110: 1622–6.

84. Mousavi N, Czarnecki A, Kumar K, et al. Relation of biomarkers and cardiac magnetic resonance imaging after marathon running. Am J Cardiol 2009;103:1467–72.

85. Hanssen H, Keithahn A, Hertel G, et al. Magnetic resonance imaging of myocardial injury and ventricular torsion after marathon running. Clin Sci 2011;120:143–52.

86. O'Hanlon R, Grasso A, Roughton M, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:867–74.

87. Kwong RY, Sattar H, Wu H, et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. Circulation 2008;118: 1011–20.

88. Mahrholdt H, Wagner A, Judd RM, et al. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J 2005;26:1461–74.

89. Babu-Narayan SV, Goktekin O, Moon JC, et al. Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries. Circulation 2005;111:2091–8.

90. La Gerche A. Can intense endurance exercise cause myocardial damage and fibrosis? Curr Sports Med Rep 2013;12:63–9.

91. Neilan TG, Januzzi JL, Lee-Lewandrowski E, et al. Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. Circulation 2006; 114:2325–33.

92. Middleton N, Shave R, George K, et al. Left ventricular function immediately following prolonged exercise: a meta-analysis. Med Sci Sports Exerc 2006;38:681–7.

93. McGavock JM, Warburton DE, Taylor D, Welsh RC, Quinney HA, Haykowsky MJ. The effects of prolonged strenuous exercise on left ventricular function: a brief review. Heart Lung 2002;31: 279–92, quiz 293–4.

94. La Gerche A, Claessen G, Dymarkowski S, et al. Exercise-induced right ventricular dysfunction is associated with ventricular arrhythmias in endurance athletes. Eur Heart J 2015;36:1998–2010.

95. Qureshi WT, Alirhayim Z, Blaha MJ, et al. Cardiorespiratory fitness and risk of incident atrial fibrillation: results from the Henry Ford Exercise Testing (FIT) Project. Circulation 2015;131:1827–34.

96. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. Circulation 2008;118:800–7.

97. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. Europace 2009;11:1156–9.

98. Thompson PD. Physical fitness, physical activity, exercise training, and atrial fibrillation: first the good news, then the bad. J Am Coll Cardiol 2015;66:997–9.

99. Kroger K, Lehmann N, Rappaport L, et al. Carotid and peripheral atherosclerosis in male marathon runners. Med Sci Sports Exerc 2011;43:1142–7.

100. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA 2014;311: 271–8.

101. Farahmand BY, Ahlbom A, Ekblom O, et al. Mortality amongst participants in Vasaloppet: a classical long-distance ski race in Sweden. J Intern Med 2003;253:276–83.

102. Maessen MF, Hopman MT, Verbeek AL, Eijsvogels TM. Dose of jogging: mortality versus longevity. J Am Coll Cardiol 2015;65:2672–3.

103. Zilinski JL, Contursi ME, Isaacs SK, et al. Myocardial adaptations to recreational marathon training among middle-aged men. Circ Cardiovasc Imaging 2015;8:e002487.

104. Bhella PS, Hastings JL, Fujimoto N, et al. Impact of lifelong exercise "dose" on left ventricular compliance and distensibility. J Am Coll Cardiol 2014;64:1257–66.

105. Karvonen MJ, Klemola H, Virkajarvi J, Kekkonen A. Longevity of endurance skiers. Med Sci Sports 1974;6:49–51.

106. Clarke PM, Walter SJ, Hayen A, et al. Survival of the fittest: retrospective cohort study of the longevity of Olympic medalists in the modern era. BMJ 2012;345:e8308.

107. Marijon E, Tafflet M, Antero-Jacquemin J, et al. Mortality of French participants in the Tour de France (1947-2012). Eur Heart J 2013;34:3145–50.

108. Kettunen JA, Kujala UM, Kaprio J, et al. All-cause and disease-specific mortality among male, former elite athletes: an average 50-year follow-up. Br J Sports Med 2015;49:893–7.

109. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol 2013;62:1290–7.

110. Doll JA, Hellkamp A, Ho PM, et al. Participation in cardiac rehabilitation programs among older patients after acute myocardial infarction. JAMA Intern Med 2015;175:1700–2.

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