

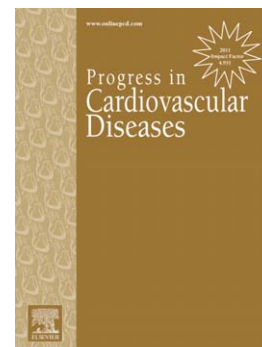
Accepted Manuscript

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PII: S0033-0620(14)00172-8
DOI: doi: [10.1016/j.pcad.2014.11.004](https://doi.org/10.1016/j.pcad.2014.11.004)
Reference: YPCAD 633

To appear in: *Progress in Cardiovascular Diseases*



Please cite this article as: O'Keefe James H., Lavie Carl J., Guazzi Marco, Part 1: Potential Dangers of Extreme Endurance Exercise: How Much is Too Much? Part 2: Screening of School-age Athletes, *Progress in Cardiovascular Diseases* (2014), doi: [10.1016/j.pcad.2014.11.004](https://doi.org/10.1016/j.pcad.2014.11.004)

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Part 1: Potential Dangers of Extreme Endurance Exercise:**How Much is Too Much?****Part 2: Screening of School-age Athletes**

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Word count: 4,209; not including references

Key Words: Exercise, cardiovascular, longevity, atrial fibrillation, physical activity, running

No Conflicts

Abbreviations

AF - Atrial Fibrillation

ARVD - Arrhythmogenic Right Ventricular Dysplasia

BNP - B-type natriuretic peptide

CAC – Coronary Artery Calcification

CHD - Coronary Heart Disease

CT – Computed Tomography

CV – Cardiovascular

CRF – Cardiorespiratory Fitness

ECG – Electrocardiogram

HCM - Hypertrophic Cardiomyopathy

MI – Myocardial Infarction

PA – Physical Activity

RA / LA – Right and Left Atria

RV – Right Ventricle

SCD – Sudden Cardiac Death

US – United States

VT - Ventricular Tachycardia

Abstract

The question is not whether exercise is or isn't one of the very best strategies for improving quality of life, cardiovascular (CV) health and longevity—it is. And there is no debate as to whether or not strenuous high-intensity endurance training produces an amazingly efficient, compliant, and powerful pump—it does. The essence of the controversy centers on what exactly is the ideal pattern of long-term physical activity (PA) for conferring robust and enduring CV health, while also optimizing life expectancy. With that goal in mind, this review will focus on the question: “Is more always better when it comes to exercise?” And if a dose-response curve exists for the therapeutic effects of PA, where is the upper threshold at which point further training begins to detract from the health and longevity benefits noted with moderate exercise? The emerging picture from the cumulative data on this hotly debated topic is that moderate exercise appears to be the sweet spot for bestowing lasting CV health and longevity. However, the specific definition of moderate in this context is not clear yet.

Part 1*Exercising for Peak Fitness versus Health and Longevity*

Physical exercise when performed regularly is one of the best strategies for enhancing quality of life, improving CV health and lengthening life expectancy.¹⁻³ However, emerging scientific evidence indicates that exercise practices that are ideal for conferring CV health and longevity may differ from the high-intensity, high-volume endurance training programs that are effective for developing peak cardiac performance and elite-level cardiorespiratory fitness (CRF).⁴ Progressively enhancing CRF levels from low to moderate to high will proportionately improve CV prognosis and overall life expectancy.⁵ However, the longevity dividends related to incremental increases in CRF plateau at about 10 metabolic equivalents (METs), with no further rise in life expectancy accruing from higher levels of CRF.⁵⁻⁷ Although a regimen of 30 minutes of moderate or vigorous physical activity (PA) on most days of the week will improve health and well-being, increasing the dose of exercise to daily multi-hour bouts of strenuous exercise will not magnify the health benefits. In fact, an evolving body of evidence suggests that excessive doses of exercise may trigger acute transient myocardial dysfunction with subsequent pathological rises in levels of cardiac troponin and B-type natriuretic peptide (BNP).⁸⁻⁹

Exercise and Survival: More is not Always Better

Epidemiological studies of healthy populations have found reverse-J-curve or U-curve

relationships for exercise dose and long-term CV health and life expectancy.¹⁰⁻¹²

Moderate exercise, as compared to a sedentary lifestyle, markedly lowers the risk for CV events and all-cause mortality.¹⁰⁻¹² However, progressively excessive regimens of chronic endurance exercise partially erase the longevity benefits associated with light and moderate exercise regimens.

The Aerobics Center Longitudinal Study

An important recent study by Lee, Lavie and colleagues focused on the mortality effects of running among a cohort of 55,000 adults ages 18 to 100 years followed for a mean of 15 years.¹³ Using comprehensive analyses that controlled for potential confounding factors, they found that runners (as compared to non-runners) had 30% and 45% lower risks of all-cause and CV mortality, respectively, with a mean improvement in life expectancy of 3-years. However, the maximal CV longevity benefits were noted with moderate doses of running: specifically 6 to 12 miles run per week, with running durations of about 50 to 120 minutes per week, with a running frequency of about 3 times per week, and a modest pace of about 6 to 7 miles per hour. Higher weekly doses of running were associated with loss of approximately one-third to one-half of the CV mortality benefits noted from the moderate doses of running. (**Figure 1A and 1B**)

The Copenhagen City Heart Study

In this prospective longitudinal study, 1,098 healthy joggers and 3,950 healthy non-joggers were followed for 12 years.¹⁴ The cohort of individuals jogging 1 to 2.4 hours per week had a 50% lower mortality rate compared to the sedentary control group. In this study, the optimal frequency of jogging was from 2 to 3 times per week, and the optimal running speed was either a slow or average pace. When the joggers were divided into 3 groups—light, moderate, or strenuous—according to running dose (as calibrated by pace, jogging duration, and frequency of runs), a U-shaped association between all-cause mortality and running dose was apparent. Light and moderate joggers had lower mortality rates than sedentary people; in contrast, strenuous runners had a mortality rate statistically similar to the sedentary group. (**Figure 2**)

Exercise Dose-Response Curve among Coronary Disease Patients

A study utilizing the National Walkers' and Runners' Health Studies database followed 2,377 survivors of myocardial infarction (MI) with the goal of assessing the dose-response relationship between exercise and long-term CV mortality.¹ Compared to a sedentary lifestyle, a regular regimen of running or walking was associated with progressive dose-dependent reductions in CV mortality. Maximal benefits, including up to 65% reductions in CV mortality, were seen among cohorts running 20 to 30 miles (32 to 48 km) per week, or walking 35 to 45 miles (56 to 73 km) per week. However, for cohorts who were exercising above these thresholds, much of the CV mortality benefit

was lost in a U-curve pattern. (**Figure 3**) Of interest, this data set from the National Walkers' and Runners' Health Studies confirmed prior reports indicating that the CV longevity benefits of walking and running were equal as long as the number of calories burned during exercise—energy expenditures—were equivalent.¹ For example, the duration of exercise required to burn 300 calories will be about twice as long for walking (about 50 to 60 minutes) compared to jogging (about 25 to 30 minutes).

Another very recent cohort study reported a reverse-J-curve pattern for exercise among 1038 individuals with stable coronary heart disease (CHD).² This study also found that inactive individuals were at the maximum risk for adverse health outcomes, with the moderate exercise cohort at the lowest risk. Intermediate in risk was the most physically active cohort (those doing strenuous exercise on a daily basis), who displayed a risk of CV mortality that was higher than the moderately active cohort, but not as high as the sedentary cohort. Over the 10-year follow-up period, that study found that the sedentary cohort was at 2-fold increased risk of MI or stroke and 4-fold higher risk of all-cause mortality compared with the moderately active group. However, the cohort who performed strenuous exercise on a nearly every day basis was also at higher risk—showing a 2-fold risk of fatal MI or stroke compared to the moderately active cohort.²

Exercise and Atrial Fibrillation

A growing number of epidemiological and observational studies consistently report strong statistically significant associations between chronic high-intensity endurance exercise and a higher risk for atrial fibrillation (AF).¹⁵⁻¹⁸ The impact of habitual exercise on the risk of AF, similar to the risk of early mortality, appears to also be nonlinear. Moderately active individuals have lower rates of AF compared to sedentary people; however higher rates of AF (in a J-curve pattern) are seen among individuals getting excessive chronic doses of vigorous, high-intensity exercise.¹⁷⁻¹⁸

A recent population-based cohort study evaluated the link between exercise and the risk of AF among 44,410 Swedish males.¹⁷ The researchers reported that intense exercise of more than 5 hours per week at age 30 years heightened the risk of developing AF later in life. In contradistinction, moderate-intensity exercise, such as walking or recreational cycling, during middle age decreased the risk of AF.¹⁷ In a similar prospective observational study of older men and women (mean age 73 years), moderate-intensity exercise like walking reduced the risk for AF by about 33%.¹⁸ However, a reverse J-shaped relationship was again apparent for exercise intensity showing that extreme exercise increased risk of AF compared to moderate exercise (**Figure 4**). Yet another recent and large cohort study, this one evaluating 52,755 long-distance cross-country skiers competing in a yearly 90-km race in Sweden, found higher rates of arrhythmias including AF among the men and women who had the fastest finishing times and the greatest number of completed cross-country skiing races.¹⁵ Fortunately, the risk of AF seems to resolve or substantially diminish with detraining and moderation of the excessive exercise dosing, likely due at least in part to normalization

of the autonomic tone.¹⁹

Marathon Running and CV Health

The number of individuals in the United States (US) running in marathons has increased 25-fold over the past 4 decades.³ Despite the excellent risk factor profiles and the generally superb CRF of long-distance runners, race-related cardiac deaths among marathon runners occur regularly, albeit rarely.²⁰ Surprisingly, long-term marathon running has in some studies been linked to accelerated, not diminished, coronary plaque development. Schwartz et al²¹ discovered that on coronary angiography, veteran endurance male runners (who had run one or more marathons each year for 25 consecutive years) had significantly greater accumulations of both hard and soft coronary plaque compared to control group of sedentary age-matched men. **(Figure 5)**

Female Marathon Resilience

Schwartz and colleagues studied both genders among the Twin Cities Marathon participants in recent decades, and found that among 25 female veteran marathoners (unlike their male marathoner counterparts) did not show an increase in the coronary plaque burden compared to a control group of sedentary women (Schwartz RS and O'Keefe JH, unpublished observations in the female marathoners).²¹ Intriguingly, the per capita incidence of race deaths among marathoners is approximately 5-fold higher for men than women.²⁰ A recent study of over 90,000 marathon finishers found that

women tend to pace themselves during a race better than men do.²⁰ Women marathon runners are much more likely than men to maintain a steady, less pressured, pace throughout the race, and thus perhaps are also less likely to break down physically during the event.²²

Cardiac Overuse Injury

We have suggested the term “cardiac overuse injury” to describe the constellation of heart abnormalities that can arise among otherwise healthy endurance athletes. Many veteran aerobic athletes have personal experience with orthopedic overuse injuries such as plantar fasciitis, Achilles tendonitis, shin splints, tennis elbow and patellar chondromalacia. Both categories of overuse injury—orthopedic and cardiac—develop as a consequence of a high-volume and/or high-intensity training regimen.^{3, 10} However, orthopedic overuse injuries tend to be more self-limiting, whereas cardiac overuse injury, if sustained over prolonged periods of training and racing, can predispose to ominous outcomes, including dangerous cardiac arrhythmias, premature aging of the heart, accelerated coronary plaque formation, myocardial fibrosis, plaque rupture with acute coronary thrombosis, and, rarely, even sudden cardiac death (SCD).¹¹

As in orthopedic overuse injuries, repetitive micro-trauma causes cardiac overuse injuries, which often present with subtle symptoms and progress gradually. Overuse injuries of all types are challenging to diagnose and treat, and often become chronic

ailments in part because the afflicted athletes are often reluctant to de-escalate their training regimens.

How Do Cardiac Overuse Injuries Occur?

The heart has a tremendous capacity to adapt to chronic exercise demands. Indeed, many positive CV adaptations occur with long-term PA; these are essential for improved fitness and tend to promote good CV health. With exercise the heart grows stronger and more functional through adaptive remodeling—which involves a balance between the break down and rebuilding of myocardial tissue.

Higher doses of aerobic exercise are associated with incrementally better CRF, as well as dose-dependent improvement of many CV risk factors including abdominal obesity, glucose metabolism, and high-density lipoprotein cholesterol. Additionally, masters level endurance athletes show youthful levels of left ventricular compliance.²³

An “arms race” among endurance athletes has led to progressively more unreasonable training regimens and races in recent years. For example, Race Across America (RAAM) is a non- stop transcontinental bicycle race; Self-Transcendence is a 3100-mile

run, and Trans Europe is a footrace of about 3,000 miles.²⁴ (**Figure 6**) The director of *Boundless*, a television show that follows two athletes as they compete in some of the world's toughest endurance challenges, was quoted "I want you guys to enter races where you almost die, but still make it to the finish line."²⁵

Some individuals may be more prone to cardiac overuse injuries due to genetic predisposition, existing cardiac disease or CV risk factors, lifestyle issues such as excess alcohol intake, psychosocial stress, inadequate rest and recovery, suboptimal diet, or use of performance enhancing agents like anabolic steroids, or amphetamines. Importantly, aging predisposes to cardiac overuse injury just as it does for orthopedic overuse injuries. Thus, moderating exercise to avoid chronic ultra-endurance efforts may be especially relevant for individuals beyond 45 or 50 years of age. Competitive athletes often train and race even when they are fighting off illnesses, such as influenza and other potentially cardio-toxic viral infections, which also might predispose to CV damage. All of these issues remain hypothetical, and will require future research for clarification.

Adverse CV Remodeling

An animal model of chronic high-intensity endurance exercise training forced rats (using tail shocks if their pace slowed) to run vigorously and continuously for 60 minutes daily during a 4-month span.^{8, 26} The running rats developed ventricular hypertrophy, and

fibrosis (collagen deposition) in the right and left atria (RA and LA), the right ventricle (RV) and interventricular septum. Ventricular tachycardia (VT) was inducible in 42% of the running rats compared to 6% of the sedentary rats ($P=.05$). Subsequently, after the forced daily running regimen was terminated, the fibrotic changes in the heart partially regressed to normal by 8 weeks. This animal study found that daily strenuous uninterrupted running reproduced the proarrhythmic adverse cardiac remodeling observed in some ultra endurance athletes.^{8, 26}

Resting cardiac output is about 5 L/min, but is capable of increasing during vigorous exercise 5-fold to about 25 L/min (often much higher yet in elite endurance athletes),¹⁸ causing acute dilation of the LA, RA, and RV. This recurrent stretching of the myocardial fibers under conditions of high oxidant stress and sustained elevations in catecholamines may eventually induce adverse structural changes also, especially in the low pressure, pliable cardiac chambers. Multiple studies show dilatation and patchy scarring of the RV, ventricular septum, and atria in some veteran endurance athletes.¹⁵⁻

16, 27-28

La Gerche et al²⁹ evaluated a group of 40 highly trained athletes competing in endurance events, including marathons (mean time to completion, 3 hours), half-ironman triathlons (5.5 hours), full-ironman triathlons (11 hours), and alpine bicycle races (8 hours). These demanding endurance exercise efforts triggered rises in

biomarkers of myocardial injury (troponin and BNP), which were proportional to immediate post-race transient reductions in RV systolic function by echocardiography.²⁹

Multiple studies have reported that endurance athletes who have symptoms of arrhythmias are much more likely to show RV dilation and decreased RV ejection fraction.³⁰⁻³¹ Notably, during extreme and sustained high-level exercise, some individuals show marked elevations in pulmonary artery pressures of up to 80 mm Hg.³² A few small studies have reported myocardial scarring (as detected by late gadolinium enhancement on magnetic resonance imaging/MRI) in the ventricular septum, with an incidence ranging from 12 to 50% among middle-aged veteran ultra-endurance athletes.^{29, 33-34}

Additionally, ventricular ectopy, including VT,³⁵ can occur in endurance athletes, even among highly fit individuals.^{20, 30} The ventricular ectopy in endurance athletes typically arises from the RV or the interventricular septum.^{30-31, 36-38} Patchy myocardial fibrosis (scar tissue) resulting from cardiac overuse injury could provide the substrate for ventricular irritability and reentry arrhythmias.^{30, 39} However, as La Gerche and colleagues⁴⁰ have recently reviewed, competitive athletes may have more arrhythmias, but overall may still have more favorable longevity due to other beneficial effects of training.

Risk Stratification for Endurance Athletes

To date, no screening strategy has been found to be effective for detecting CV pathologic changes due to excessive endurance exercise. In symptomatic individuals who are complaining of arrhythmias, or other CV symptoms, using echocardiography or MRI to identify adverse structural remodeling and substrate for arrhythmias is theoretically logical.³⁷ Computed tomography (CT) to screen for and score coronary artery calcification (CAC) may be useful and is much less expensive than MRI and echocardiography. CT-CAC scoring may be especially useful for endurance athletes over age 45 or 50 years. Exercise testing is generally not a sensitive strategy for screening ultra endurance athletes. Cost-effectiveness and/or clinical accuracy for detecting cardiac overuse injury are not available for any testing modality.

Exercise Dosing for Maximizing CV Health and Longevity

Physical inactivity is a much more prevalent public health problem than is excessive exercise. A recent survey of 500,000 American adults reported that about 50% of people do not meet the suggested minimum exercise dose of 150 minutes per week of moderate-intensity aerobic PA.⁴¹ On the other hand, extrapolation of the Williams and Thompson¹ data-set indicate that a small minority of runners and walkers in the US may be overdosing their PA, potentially increasing the risk-to-benefit ratio of their exercise program. (**Figure 7**) People on the margins of either end of the exercise spectrum (sedentary individuals and over-exercisers) would likely improve their long-term CV

health and longevity by altering their daily PA pattern so to be in the safe moderate range.

Exercise is unequalled for its power to enhance quality of life and CV health, and in this regard can be thought of as a therapeutic agent. Thus, when prescribing exercise we should think of potential indications and contraindications, and customize the prescription to the individual. As with any potent therapy, ascertaining the safe and effective dose range is vitally important—an inadequately low dose may not confer full benefits, while an overdose may cause hazardous adverse effects that outweigh its benefits. Thankfully, the exercise dose-response range that is safe and effective for optimizing CV health and longevity is broad. Desperately needed public health efforts to reduce physical inactivity and prolonged periods of sitting are underway and gaining momentum. Yet, attention should also be focused on delivering the message that even light and moderate doses of exercise can bestow powerful health benefits, and it is very possible that excessively strenuous chronic exercise may erode some of the health dividends of less extreme PA.⁴²

The emerging data suggest that it may be sensible to limit chronic vigorous exercise to no more than about 60 minutes per day.^{1-3, 13, 17} More support for this recommendation comes from a recent trial of 60 men with stable CHD who were randomized to strenuous aerobic exercise sessions lasting either 30 or 60 minutes.²⁷ The 30-minute exercise bouts enhanced arterial elasticity yet generated only minimal oxidative stress.

In contrast, the 60-minute sessions transiently stiffened blood vessels and markedly increased the oxidant stress, especially among men over age 50 years.²⁷

A cumulative weekly dose of strenuous exercise of not more than about 5 hours has been suggested in several studies to be near the safe upper limit for conferring optimal long-term CV health and overall longevity.^{1-3, 10-13, 17, 27} It also appears to be beneficial to avoid performing high-intensity exercise on an everyday basis, and to instead take 1 or 2 days a week off to allow the body and heart to rest and recover.^{1-3, 10-13, 17}

Summary of Part 1

If one's goal is to decrease risk of CV death and improve life expectancy, going for a short, leisurely jog a few times per week is adequate. High-volume, high-intensity training is not just unnecessary—very high doses of chronic PA may diminish some of the remarkable CV benefits conferred by moderate exercise. In fact, based upon the best data available, a running dose that appears to be highly favorable for reducing CV mortality (though far below the dose for maximizing CRF) is: jogging about 3 days per week, with a cumulative distance of 6 miles per week, at a pace of 6 or 7 miles per hour (corresponding to 8.5 to 10 minutes per mile). Many people would perceive this to be a goal that is reasonable, achievable and sustainable.

Part 2:***Screening of School-age Athletes***

SCD in young competitive athletes or older athletes is a tragic event. In most cases of this type, SCD is secondary to malignant ventricular arrhythmias that is caused by underlying structural CV disease.¹⁻⁴ Cardiomyopathies have been consistently implicated as the leading cause of SCD in young competitive athletes, especially with hypertrophic cardiomyopathy (HCM) accounting for over a third of the cases in the US, whereas arrhythmogenic right ventricular dysplasia (ARVD) causes almost a quarter of the fatal cases in Italy.⁴³

A major issue is whether there should be a preparticipation screening for athletes and what this should entail, with quite different recommendations currently coming from different countries, such as the US and Italy.⁴³⁻⁴⁷ Currently, medical evaluations of competitive athletes prior to competition offers the potential to identify asymptomatic athletes with potentially life-threatening CV disorders and to prevent SCD through disqualification from highly competitive sports. Certainly, SCD in young competitive athletes are highly visible and emotional events with considerable impact on physicians and the lay communities. However, the magnitude of this topic from a public health perspective has been hotly debated.

Analysis of Recent US Deaths

Recently, Maron and colleagues⁴⁴ reviewed SCD in young competitive athletes (n=1,866) from 1980-2006. In this large national registry, SCD was predominantly due to CV disease (56%); the most common being HCM (36%) and coronary artery anomalies (17%). In this cohort, 29% of the events occurred in African Americans, 54% in high school students and 82% with physical exertion. The absolute number of events was relatively low (<100 per year on average), although somewhat higher than previously estimated. The authors concluded that their data were quite relevant to the current debate about preparticipation screening with electrocardiograms (ECGs).

Benefits of Preparticipation Screening in Italy

"He who saves a single life saves the whole world"

Talmud Sanhedrin 4:5⁴⁸

Italian law mandates that every participant engaged in competitive sports activity must undergo a clinical evaluation and obtain eligibility.⁴³⁻⁴⁹ In fact, a nationwide systematic screening program, which was largely based on a preparticipation 12-lead ECG, was launched in 1982. Several years ago, Corrado and colleagues⁴³ reported that following this intervention program, CV deaths fell by 44% in the early screening program (P=0.001) and by 79% in the late screening program (P=0.001). During the study period, 2% of athletes were disqualified for CV diseases. The major fall in SCD in this analysis was secondary to a low incidence of SCD from cardiomyopathies.

Comparison of US and Italian Experience with SCD in Athletes

Maron and colleagues⁴⁵ recently analyzed the SCD rate among competitive athletes in Minnesota compared with that from Italy. They demonstrated that CV death in Veneto, Italy exceeded that in Minnesota for the 11 year period (1993-2014). They concluded that despite quite different preparticipation screening (history and physical exam in the US without any formal diagnostic testing versus ECG testing plus examination in Italy), the SCD rate did not differ considerably, suggesting that their data did not support a lower mortality rate associated with preparticipation screening programs involving routine ECG and examinations by training personnel.

Experience in Israel

Several years ago, Steinvil and colleagues⁴⁶ reported the Israel experience before and after an ECG screening program for athletes. They reported except for a spike in the Israel SCD event rate in 1995/96, the rate of SCD in Israel was similar before and after the Israeli Sports Law was implemented in 1997/98 and was similar to that noted in Italy and Minnesota (**Figure 8**). They concluded that mandatory ECG screening of athletes had no apparent effect on the risk of SCD in athletes.

Major Recommendations from the US and Europe

The various recommendations from the US and Europe have recently been reviewed, including the Bethesda Conference #36 and the European Society of Cardiology Consensus Recommendations with the differences in the recommendations summarized in **Table 1**.^{47, 50} Clearly, the European Society of Cardiology Guidelines are considerably more restrictive than the US (Bethesda Conference #36) Guidelines. Italy has particularly restricted guidelines, including screening all athletes yearly with Sports Medicine history, physical examination and ECG. On the other hand, in the US, athletes obtained their own physician's clearance, which is generally not very intensive, but often includes a brief history and physical examination.

It seems apparent at some point in time to consider assembling updated recommendations from experts from around the world to determine sports eligibility and criteria for disqualification that includes both the US and European perspectives that is applicable to the Global Sports Medicine Community. Certainly, at present, the cost-effectiveness of more formal testing, including ECG and, even more so, for echocardiography, is questionable.^{47, 50} Despite this, there may be some subgroups (e.g., possibly African American basketball players), who may be at higher risk and could benefit from more intensive testing, although this hypothesis is currently unproven.

At present, it is clear that HCM cannot be cleared. Long Congenital QT Syndrome (defined as QTc >0.47 seconds in males and 0.48 seconds in females in US or 0.44 seconds and 0.46 seconds, respectively in Europe) cannot be cleared. Brugada Syndrome and Catecholamine Polymorphic VT cannot be cleared. Marfan's cannot be cleared when the aortic root is >40 mm, as well as those with Marfan's and either moderate-severe mitral regurgitation or a family history of aortic dissection or SCD. In Wolff-Parkinson-White Syndrome, clinicians could consider electrophysiologic testing and need for radiofrequency ablation for symptoms or for AF. Severe aortic stenosis and severe aortic regurgitation generally cannot be cleared, whereas severe mitral regurgitation with preserved left ventricular function in asymptomatic patients generally can be cleared. Nevertheless, further defining these recommendations is clearly needed.^{47, 50}

Figure Legends:

Figure 1A and 1B: Cardiovascular Mortality by Running Distance, Frequency, Total Amount, and Speed. Participants were classified into 6 groups: nonrunners and 5 quintiles of each running distance, frequency, total amount, and speed. All hazard ratios (HRs) were fully adjusted for baseline risk factors. The bars indicate 95% CI, and HRs are shown next to the bars. MET = metabolic equivalent.¹³ Permission received.

Figure 2: Mortality in light, moderate and strenuous joggers compared to sedentary non-joggers.¹⁴ Permission received.

Figure 3: Risk of death during follow up as a function of exercise-related energy expenditure. Increasingly higher doses of exercise, via walking and/or running, proportionately reduced the risk for all-cause mortality and CV mortality up to 7.2 METh/d—equivalent to running 30 miles per week, or briskly walking 46 miles per week. Higher weekly exercise efforts beyond this threshold negated the benefits noted with the exercise doses from the first four quintiles.¹ Permission received.

Figure 4: Risk of new-onset atrial fibrillation (Afib) among 5,446 older adults (> 65 years of age) as a function of exercise intensity. Low and moderate intensity exercise reduced risk of Afib; however, some of this protection was lost in the high-intensity exercise group.⁴ Permission received.

Figure 5: Male marathoners had significantly more total coronary plaque volume, non-calcified plaque volume and calcified plaque volume compared to sedentary control subjects.⁴ Permission received.

Figure 6: During the TransEurope FootRace in 2009 15 runners were followed with serial magnetic resonance imaging brain scans before, during and after this 4,487 km ultramarathon. The data depicted here showed 6% mean reduction in grey matter. This decrease in brain volume returned to baseline by 8 months after the race.²⁴ Permission received from Biomed Central, original publisher of Figure 2.

Figure 7: About half of the population does not meet the minimum recommended amount of physical activity per week. However, a small minority, about 2.5%, may be overdoing aerobic exercise.^{1, 41} Figure made from information in manuscript.

Figure 8 – The Italian study (4) (pink graph) concluded that electrocardiography (ECG) screening (started in 1982) significantly reduced the incidence of sudden cardiac death by comparing the sudden death in the 2-year pre-screening period (A to B) with the post-screening period (B to F). The present study is depicted by the green graph. We compared the 12 years before screening (C to E) with the 12 years after the onset of mandatory ECG screening (E to G). Had we limited our comparison of the postscreening period to the 2-year period preceding the enforcement of screening in Israel (D to E vs. E to G, as performed in the Italian study), we would have concluded erroneously that screening saved lives of athletes in Israel. The study from Minnesota (19) (yellow graph) shows a low mortality rate in a population of athletes not undergoing systematic ECG screening.⁴⁶ Permission received.

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ACCEPTED MANUSCRIPT

Figure 1A

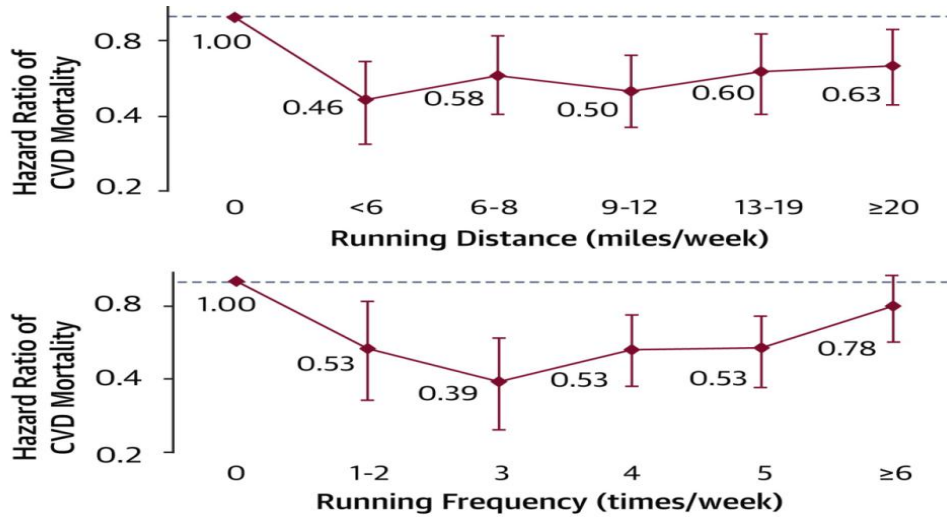


Figure 1B

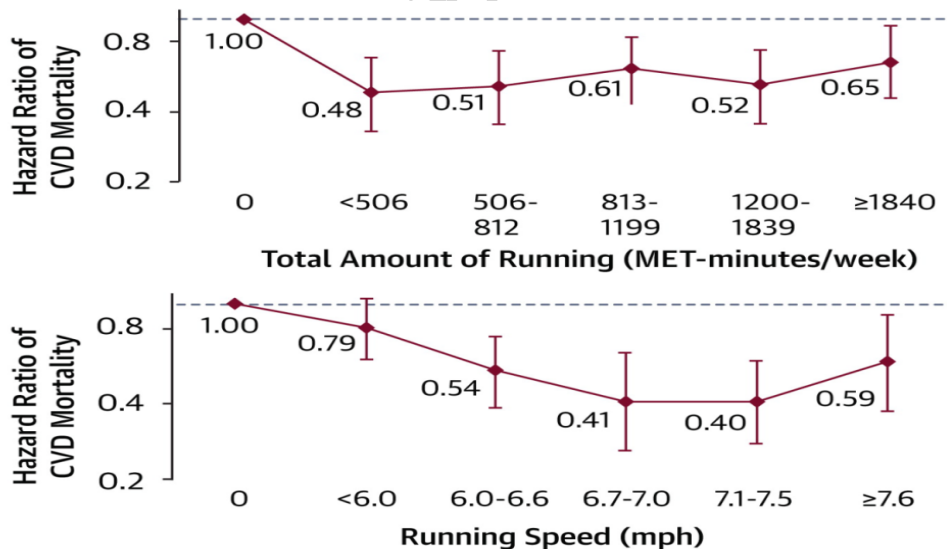
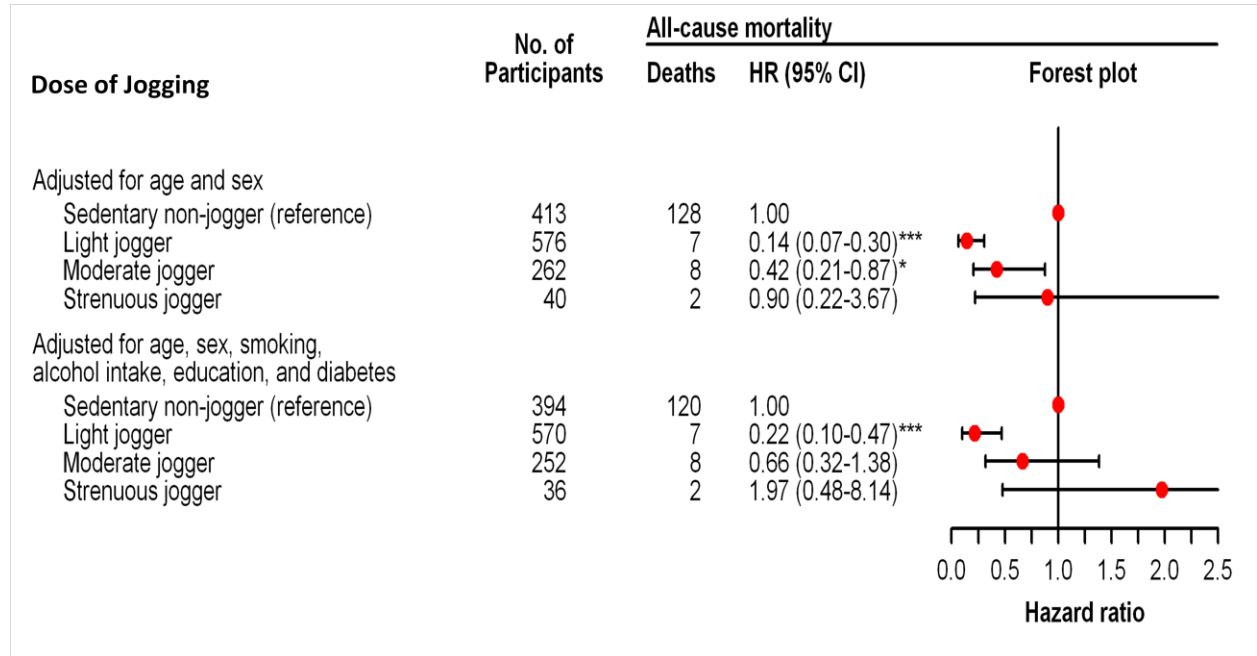


Figure 2



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Figure 3

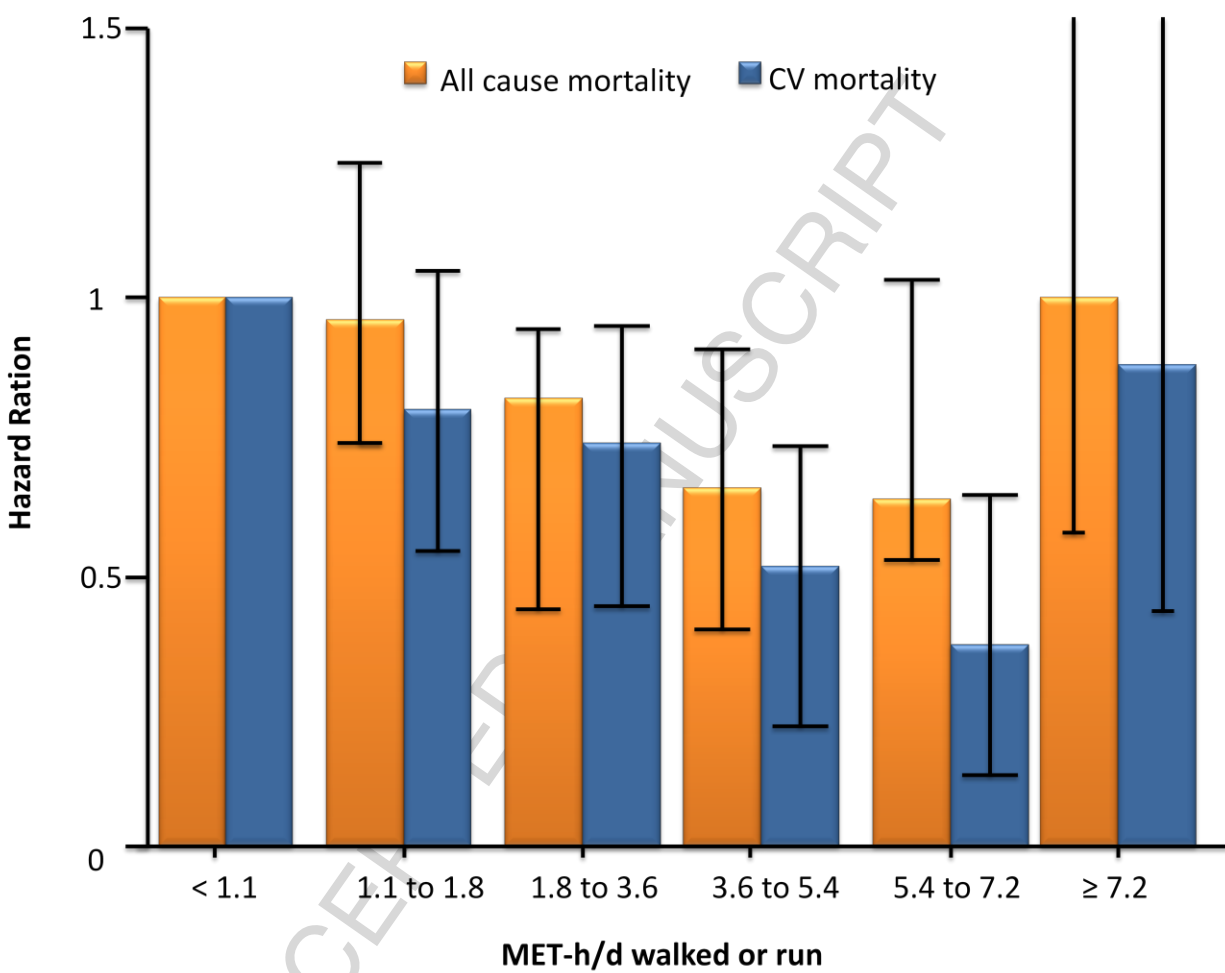
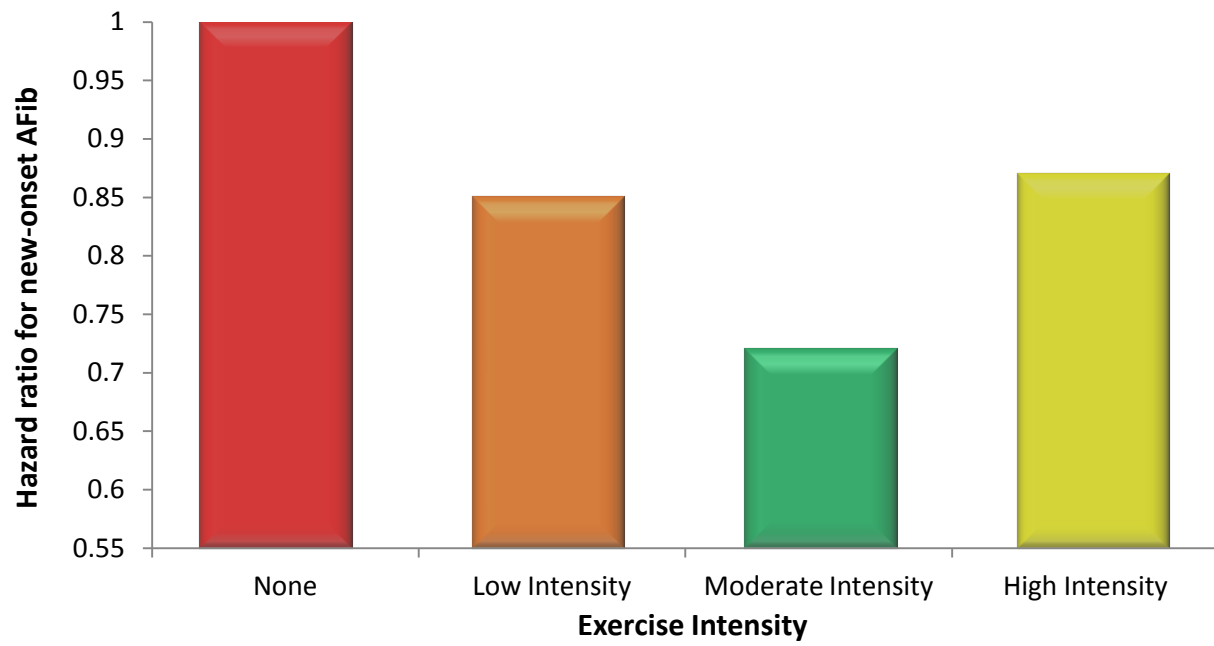
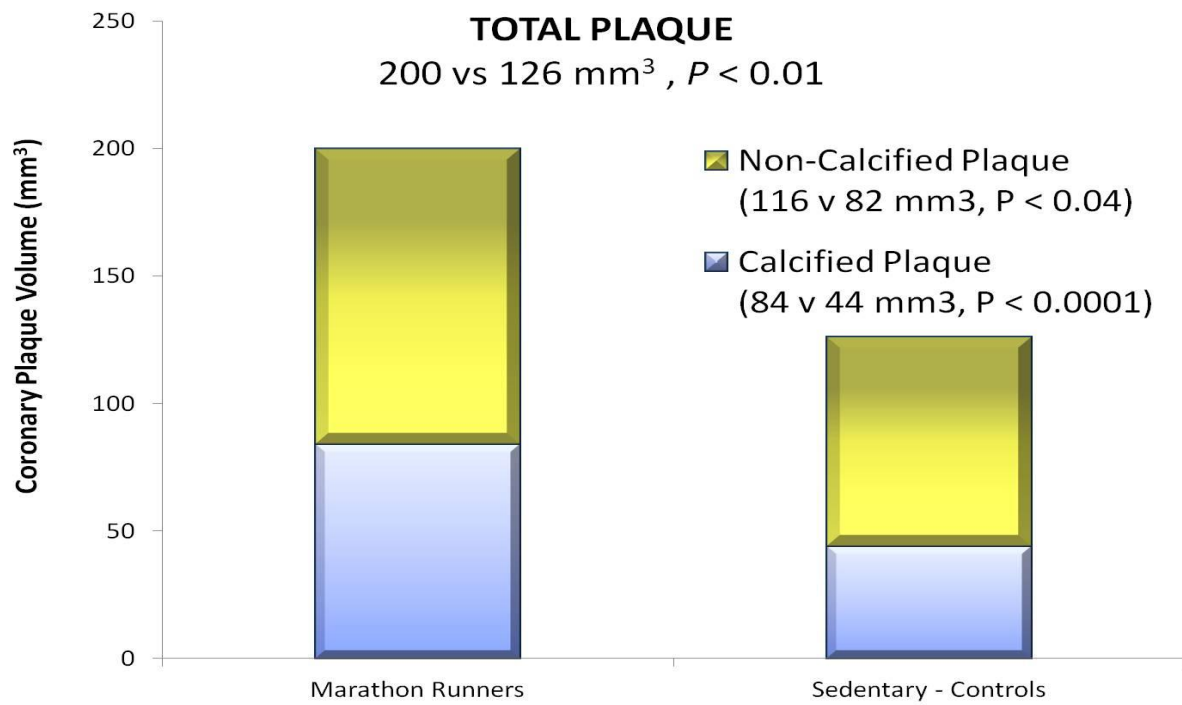


Figure 4



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Figure 5



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Figure 6

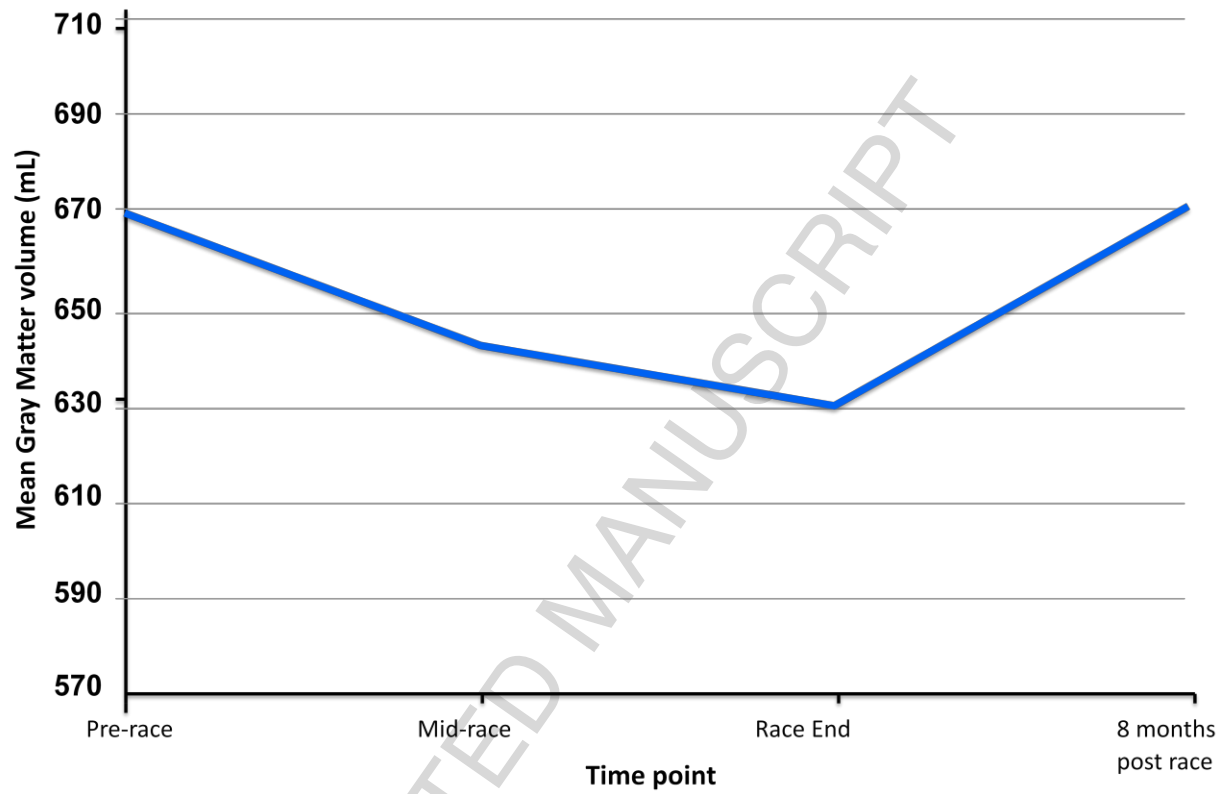
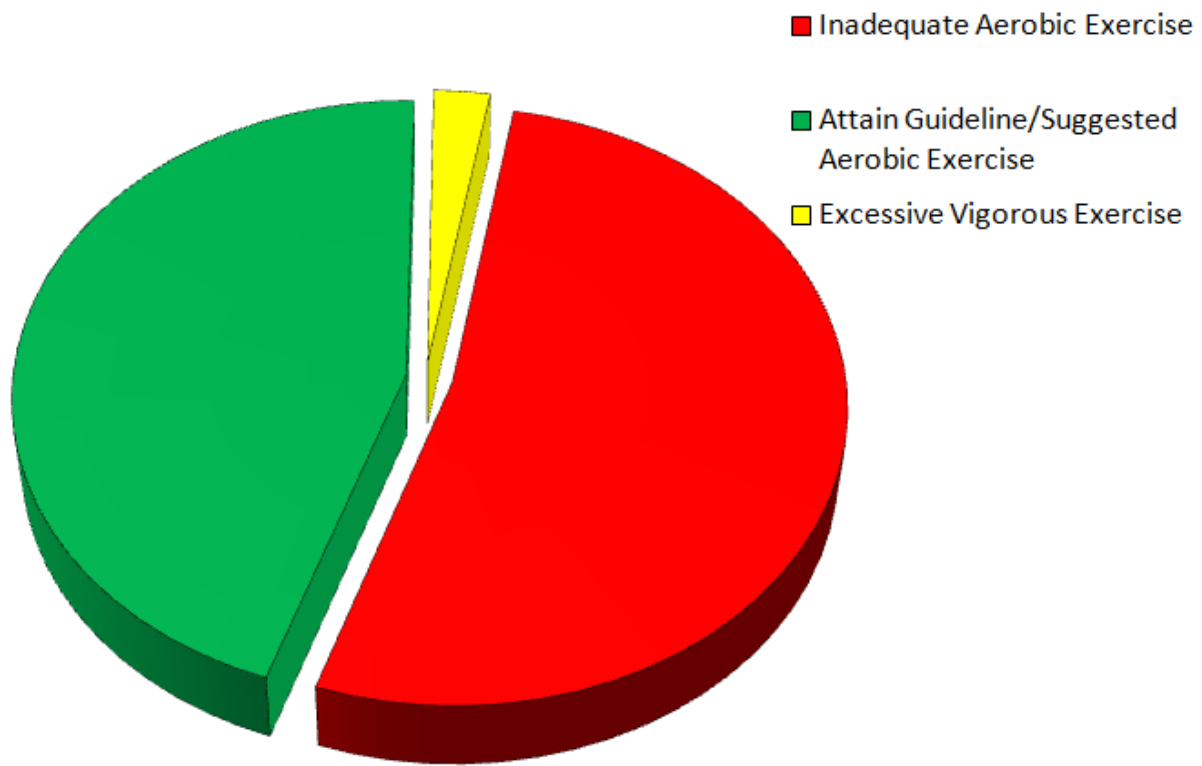
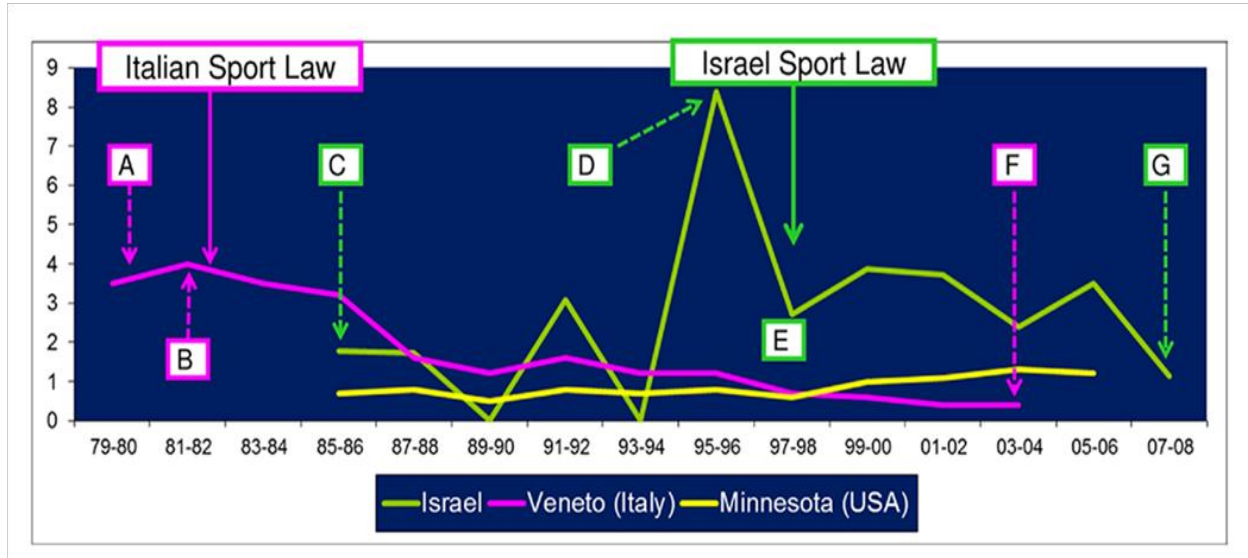


Figure 7



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Figure 8



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Table 1. Summary of Selected Differences Between BC#36 and ESC Recommendations for Competitive Athletes with Selected CV Abnormalities.

	Clinical Criteria and Sports Permitted	
	BC#36	ESC
Gene carries without phenotype (HCM, ARVC, DCM, Ion channel diseases*)	All sports	Only recreational sports
LQTS	> 0.47 s in male subjects, > 0.48 s in female subjects Low-intensity competitive sports	> 0.44 s in male subjects, > 0.46 s in female subjects Only recreational sports
Marfan syndrome	If aortic root < 40 mm, no MR, no familial SD, then low-moderate intensity competitive sports permitted	Only recreational sports
Asymptomatic WPW	EPS not mandatory All competitive sports (restriction for sports in dangerous environment)†	EPS mandatory All competitive sports (restriction for sports in dangerous environment)†
Premature ventricular complexes	All competitive sports, when no increase in PVCs or symptoms occur with exercise	All competitive sports, when no increase in PVCs, couplets, or symptoms occur with exercise
Nonsustained ventricular tachycardia	If no CV disease, all competitive sports If CV disease, only low-intensity competitive sports	If no CV disease, all competitive sports If CV disease, only recreational sports

*Long-QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia; †sports in dangerous environments are restricted, given the risk should impaired consciousness occur, such as motor sports, rock climbing, and downhill skiing.

ARVC = arrhythmogenic right ventricular cardiomyopathy; BC#36 = Bethesda Conference # 36; CV = cardiovascular; DCM = dilated cardiomyopathy; EPS = electrophysiologic study; ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; MR = magnetic resonance; PVC = premature ventricular complex; SD = sudden death; WPW = Wolff-Parkinson-White syndrome.

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