Effects of Running on Chronic Diseases and Cardiovascular and All-Cause Mortality

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Abstract

Considerable evidence has established the link between high levels of physical activity (PA) and all-cause and cardiovascular disease (CVD)–specific mortality. Running is a popular form of vigorous PA that has been associated with better overall survival, but there is debate about the dose-response relationship between running and CVD and all-cause survival. In this review, we specifically reviewed studies published in PubMed since 2000 that included at least 500 runners and 5-year follow-up so as to analyze the relationship between vigorous aerobic PA, specifically running, and major health consequences, especially CVD and all-cause mortality. We also made recommendations on the optimal dose of running associated with protection against CVD and premature mortality, as well as briefly discuss the potential cardiotoxicity of a high dose of aerobic exercise, including running (eg, marathons).

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Considerable evidence has established the link between high levels of physical activity (PA), regular exercise training (ET), and cardiorespiratory fitness (CRF) and the reduced long-term risk of various chronic diseases, including cardiovascular disease (CVD) and all-cause mortality.[1-6] Despite the known benefits of high levels of PA and ET, some evidence suggests that there may be a point of diminishing returns. In fact, there may be a threshold at which high doses of aerobic ET might detract from the remarkable health benefits of moderate ET or even induce cardiotoxicity.[7-9]

The current US guidelines for aerobic PA and ET suggest that all individuals should perform at least 150 min/wk of moderate PA, 75 min/wk of vigorous PA, or an equivalent of a combination of both.[2,10] Running is a particularly attractive form of aerobic PA and ET that is generally regarded as a popular and practical high-intensity form of vigorous ET.[11,12] Other evidence indicates that considerable benefits of aerobic PA and ET may be attained at levels well below those suggested by these national and international guidelines,[11-15] and, in fact, there may be cardiotoxicity of extreme exercise training (EET), such as prolonged, high-volume training and competing in marathons, ultramarathons, or full distance triathlons.[7-9,16]

In this review, we examine the evidence for the benefits of vigorous aerobic PA and ET, specifically running, for protection against various chronic diseases, including CVD and all-cause mortality. We also discuss the potential toxicity of a high dose of aerobic ET, including high levels of running. Finally, we make recommendations for running doses that are associated with maximal health benefits while diminishing the risk of cardiotoxicity, as well as make recommendations for advising and treating those who perform EET.

LINK BETWEEN PA, ET, CRF, AND PROGNOSIS

Considerable evidence suggests that physical inactivity, also referred to as a sedentary lifestyle, may be the greatest threat to health in the 21st century.[1-3] Despite the guidelines for PA, evidence suggests that a minority of adults in the United States and much of Western civilization are meeting these minimal PA recommendations.[1-3,17] We have previously reported that a progressive decline in PA, especially in occupational and household PA, over the past 5 decades is a primary cause of the obesity epidemic that has been spreading in our society, and this also

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ARTICLE HIGHLIGHTS

- Considerable evidence suggests that physical inactivity may be the greatest threat to health in the 21st century.
- Substantial evidence indicates that low levels of cardiorespiratory fitness may be one of the strongest risk factors for cardiovascular disease.
- Runners typically perform vigorous physical activity and have high levels of cardiorespiratory fitness.
- We reviewed data that indicate that running has benefits in the prevention of obesity, hypertension, dyslipidemia, type 2 diabetes, osteoarthritis and hip replacement, benign prostatic hypertrophy, respiratory disease, cancer, and disability.
- Running, even in quite low doses, is associated with a substantial reduction in cardiovascular and all-cause mortality.
- High doses of running (eg, marathons) have the potential for cardiotoxicity, although these risks are relatively low.
- Maximal health benefits of running appear to occur at quite low doses, well below those suggested by the US physical activity guidelines.

impacts the health of the next generation and contributes to many chronic diseases and adverse CVD outcomes.[18-21] Considerable evidence suggests that high levels of PA and ET are associated with improved clinical outcomes, beyond those expected on the basis of effects on traditional risk factors for CVD, suggesting that other factors (eg, autonomic function, preconditioning, and endothelial function) might also explain the marked benefits noted.[1-3,5] This evidence comes from studies evaluating the effects of both leisure time PA and occupational PA on subsequent prognosis.[1,2]

In addition, substantial evidence indicates that low levels of CRF may be one of the strongest risk factors for CVD.[1,2,4,6] In fact, preserved levels of CRF are associated with favorable prognosis in most patient groups, including those with obesity, type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidemia (DLP).[1,2,6] Patients with these disorders but with a favorable level of CRF generally have a considerably better prognosis than do unfit individuals without these disorders.[1,2,6] Although there is an inherited non-PA component of CRF, which may contribute approximately 15% to 30% to the overall CRF level,[12,22] the major determinant of CRF is the amount and intensity of aerobic PA and ET. Although high levels of both PA and CRF predict a better prognosis, most studies indicate that CRF levels are a considerably better predictor of prognosis than are PA levels.[1,2,6]

Although this review focuses on running, it is worth noting that running is typically associated with high levels of aerobic PA, well above the metabolic equivalent (MET) level of 7, and during the maximal exercise test, runners typically have exercise capacities well above the MET level of 10, which is a level of CRF that is particularly associated with a favorable prognosis.[11,12,23-25] However, as discussed below, at least in runners, there may be a discordant relationship between CRF and prognosis.[11]

MAJOR RUNNING STUDIES

Although many studies have assessed the impact of running on chronic diseases as well as CVD and all-cause mortality, this review focuses predominantly on prospective observational databases, including published findings from the National Runners' and Walkers' Health Study,[26-43] the Running Aging Study,[44] the Copenhagen City Heart Study,[13,14] and the Aerobics Center Longitudinal Study (ACLS).[11,12] We reviewed studies published in PubMed since 2000 that included at least 500 runners and at least 5 years of follow-up so as to analyze the relationship between vigorous aerobic PA, specifically running, and major chronic diseases and/or CVD and all-cause mortality.

Impact of Running on Weight and Obesity

Williams[27-29] published several studies on the impact of running on weight and obesity. In a study of 33,480 male runners and 14,211 female runners, the body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) and waist circumference of runners who ran less than 3 km/d were significantly related to their parents' adiposity.[27] However, this relationship weakened significantly in those with higher doses of running. In fact, exceeding the minimal ET dose recommendation, runners (energy equivalent of 2-3 km/d) seemed to have a substantial reduction in the risk of inherited obesity.

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In another study of 62,042 men and 44,695 women, runners had lower BMI, and running seemed to mitigate the adverse effect of diet-induced weight gain, as assessed by both BMI and waist circumference.[28]

In addition, in a study of 15,237 walkers and 32,216 runners, walkers spent less than half the energy per week than did runners, and walkers were considerably heavier than runners.[29] During follow-up, energy expenditure decreased less for walkers than for runners. Although changes in BMI over time were associated with changes in both running and walking over time (in MET hours per day), changes in BMI were significantly greater for changes in running than for changes in walking, suggesting that a greater weight loss was achieved by running than by walking over an average prospective follow-up period of 6.2 years.

In the National Aging Study, BMI was also considerably lower in runners than in nonrunners (22.9 kg/m^2 vs 24.4 kg/m^2), which is similar to the findings of the Copenhagen City Heart Study (24.4 kg/m^2 vs 25.7 kg/m^2 in men and 22.5 kg/m^2 vs 24.5 kg/m^2 in women) and our ACLS (25.2 kg/m^2 in the lowest quintile of running time [in minutes per week] vs 23.9 kg/m^2 in the highest quintile as compared with 26.3 kg/m^2 in the nonrunners). Runners had considerably lower prevalence of overweight and obesity BMIs than did nonrunners.

Impact of Running on HTN, DLP, and T2DM

Several studies have addressed the impact of running and walking on the risk of HTN, DLP, and T2DM.[30-35] In a study of 33,060 runners and 15,945 walkers, both running and walking were associated with a lower prevalence of HTN (−4.2% and −7.2%, respectively) , hypercholesterolemia (−4.3% and −7.0%, respectively), T2DM (−12.1% and −12.3%, respectively), and coronary heart disease (CHD) (−4.5% and −9.3%, respectively) per MET hours per day.[30] In a study of 25,552 male runners and 29,148 female runners, higher intensity of running (eg, faster running paces) was associated with a lower prevalence of HTN, DLP, and T2DM independent of exercise volume and CRF level (determined by 10-km performance), suggesting that the more vigorous the exercise, the more robust the overall benefit.[31] In an analysis of 29,139 men and 11,985 women followed for 7.7 and 7.4 years, respectively, during follow-up, 2342 men (8.5%) and 499 women (4.3%) developed HTN, 3330 men (12.2%) and 599 women (5.1%) developed DLP, and 197 men (0.7%) and 28 women (0.2%) developed T2DM. Longer baseline running distances predicted lower prevalence of HTN, DLP, and T2DM in men and women. However, higher baseline CRF level, defined by 10-km performance, predicted lower prevalence of HTN, DLP, and T2DM in men and women independent of distance. Compared with the least fit men, the fittest men had a reduction in the prevalence of HTN, DLP, and T2DM by 62%, 67%, and 86%, respectively.[32] In an assessment of 62,284 male participants and 45,040 female participants, the prevalence of HTN, DLP, and T2DM decreased with greater participation in marathons independent of the annual running distance.[33]

Impact of Running on Osteoarthritis and Hip Replacement Risk

Williams[36] analyzed 74,752 runners (2004 with osteoarthritis [OA] and 259 with hip replacement) and 14,625 walkers (695 with OA and 114 with hip replacement) over a follow-up period of 7.1 and 5.7 years, respectively. Compared with those who ran less than 1.8 MET-h/d, those who ran 1.8 to 3.6 MET-h/d had 18% and 35% reduction in OA and hip replacement risk, respectively, but a higher dose of running did not produce a substantially different risk reduction. Baseline BMI, however, was strongly associated with both OA (5% increase per kg/m^2) and hip replacement (10% increase per kg/m^2) risk, and adjustment for BMI substantially diminished the risk reduction for running more than 1.8 MET-h/d: from 16.5% (P=.01) to 8.6% (P=.21) for OA and from 40.4% (P=.005) to 28.5% (P=.07) for hip replacement. Running and walking, but not other exercises, produced an equal reduction in OA and hip replacement risk.

Impact of Running Distance and Performance on Benign Prostatic Hypertrophy

In a study of 28,612 men (mean age, low to mid-40s) followed for 7.7 years, 1899 (∼6.6%) reported physician-diagnosed benign prostatic hypertrophy.[37] Both longer distance and faster

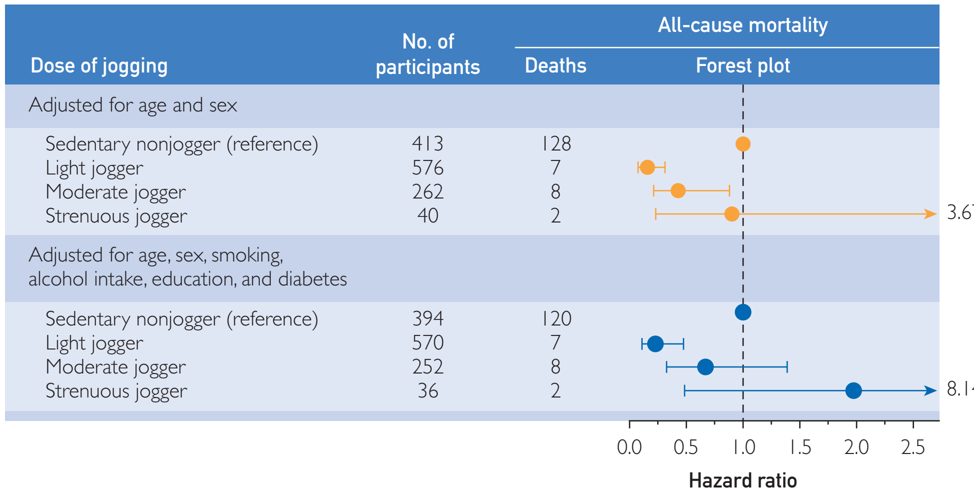


FIGURE 1. Forest plot indicating all-cause mortality in light, moderate, and strenuous joggers compared with sedentary nonjoggers. Reproduced with permission from *J Am Coll Cardiol*.[14]

running were associated with a lower risk of benign prostatic hypertrophy independent of age, BMI, and meat, fish, fruit, and alcohol intake, suggesting benefits of running in another chronic disease.

Impact of Running on Disability

In the Nationwide Runners Club (538 members and 423 healthy controls) of Northern California, individuals 50 years and older in 1985 were followed long-term for the development of disability. Survival curves for disability diverged markedly between the 2 groups during follow-up as runners approached their ninth decade of life, suggesting that running in midlife is associated with a substantial reduction in disability.[44]

Impact of Running on Respiratory Disease Mortality

Of 109,352 runners and 40,798 walkers, 236 died of respiratory disease listings in the cause and 833 died of respiratory disease related to the cause.[38] Running and walking produced an equal reduction in the risk of respiratory disease, pneumonia, and aspiration pneumonia mortality in a dose-dependent relationship and independent of age, sex, smoking status, diet, alcohol consumption, and education level. These effects also seemed to be independent of exercise effects on CVD.

Impact of Running on Cancer

Several analyses in the National Runners' and Walkers' Health Study have assessed cancer and/or cancer mortality.[39-41] In an analysis of more than 90,000 individuals, the risk of incident kidney cancer was 61% lower in those meeting exercise guideline levels, 67% lower in those meeting 1 to 2 times the recommended guideline levels, and 76% lower in those meeting 2 times or more the recommended guideline levels.[39] The risk of incident kidney cancer also increased with increasing BMI, smoking, and HTN and T2DM medications. Of 79,124 women (32,872 walkers and 46,252 runners), 111 died of breast cancer during the 11-year follow-up.[40] A similar risk reduction was seen for running and walking when adjusted for MET hours per day; however, breast cancer mortality was 42% lower for those who exercised 4.5 MET-h/wk or more than for those who performed lower levels of exercise, which persisted when adjusted for other risk factors. In a study of 111,266 runners and 42,136 walkers followed for 12 years, brain cancer mortality was the same for walkers and runners when adjusted for MET hours per day.[41] Brain cancer mortality was 43% lower for those who exercised for 1.8 to 3.5 MET-h/d and 40% lower for those who exercised for 3.6 MET-h/d or more as compared with those who performed lower levels of exercise.

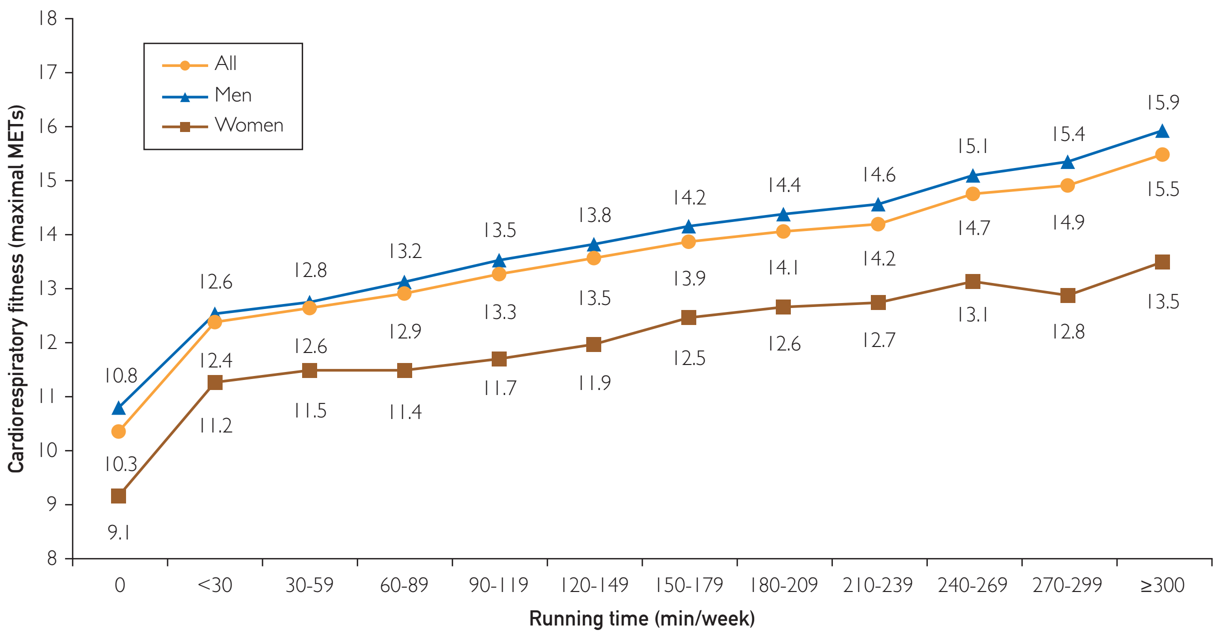


FIGURE 2. Cardiorespiratory fitness level was estimated from the final treadmill speed and grade during the maximal exercise test in a subsample of 50,995 participants. All *P* values for a linear trend across weekly running time were less than .001 after adjustment for age and sex (not in sex-stratified analyses). MET = metabolic equivalent. Reproduced with permission from *J Am Coll Cardiol*.[11]

Impact of Running on Risk of Stroke

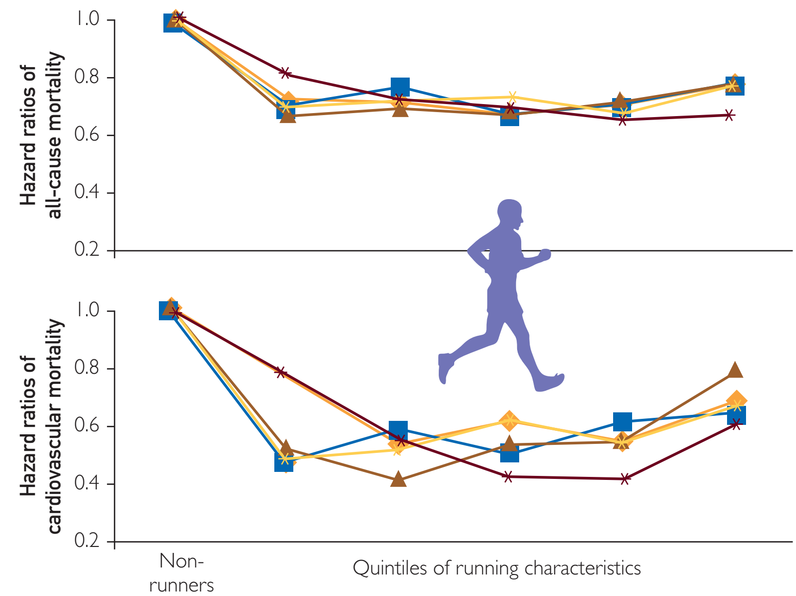
In an assessment of 29,272 male runners and 12,123 female runners followed prospectively for 7.7 years, 100 men and 19 women experienced a cerebrovascular accident (CVA).[42] For each run (running distance in kilometer per day), the age- and smoking-adjusted risk of CVA decreased by 12% and 11% in men and women, which remains significant when adjusted for T2DM, DLP, HTN, and BMI. In addition, the risk of CVA was progressively reduced with a progressive increase in running distances, which was not attributed statistically to HTN, T2DM, DLP, or BMI.

Impact of Running on CVD and All-Cause Mortality

In the Nationwide Runners Club mentioned above,[44] a total of 284 runners and 156 controls completed the 21-year follow-up. At 19 years, 15% of runners had died compared with 34% of controls. After adjusting for covariates, runners had a 39% reduction in mortality. In addition, survival curves continued to diverge markedly between the 2 groups after the 21-year follow-up as participants approached their ninth decade of life, suggesting that vigorous exercise, such as running in mid-life, is associated with a substantial reduction in mortality over time.

In a cohort of 29,721 men, Williams[26] assessed whether CRF determined by time in races (10-km footrace performance; in meters/second) predicted CHD independent of PA. In this study, CRF was found to be a significant risk factor for CHD, specifically nonfatal myocardial infarction (MI), angina pectoris, and revascularization procedures, largely independent of PA. In fact, each meter's improvement (measured in meter per second) in running performance was associated with a 44% lower risk of CHD death and nonfatal MI, 54% lower risk of nonfatal MI, 53% lower risk of angina pectoris, and 32% lower risk of revascularization procedures. Furthermore, this study found that the risk of nonfatal MI decreased linearly with higher levels of CRF determined by running performance.

In an analysis by Williams limited to those with the diagnosis of HTN (6973 walkers and 3907 runners), compared with those running or walking for less than 1.07 MET-h/d, running or



Time (min/wk)	0	<51	51-80	81-119	120-175	≥176
Distance (miles/wk)	0	<6	6-8	9-12	13-19	≥20
Frequency (times/wk)	0	1-2	3	4	5	≥6
Total amount (MET-min/wk)	0	<506	506-812	813-1199	1200-1839	≥1840
Speed (mph)	0	<6.0	6.0-6.6	6.7-7.0	7.1-7.5	≥7.6

FIGURE 3. Hazard ratios (HRs) of all-cause and cardiovascular mortality stratified by running characteristics (weekly running time, distance, frequency, total amount, and speed). Participants were classified into 6 groups: nonrunners (reference group) and 5 quintiles of each running characteristic. All HRs were adjusted for baseline age (years), sex, examination year, smoking status (never, former, or current), alcohol consumption (heavy drinker or not), other physical activities except running (0, 1-499, or ≥500 MET-min/wk), and parental history of cardiovascular disease (yes or no). All *P* values for HRs across running characteristics were less than .05 for all-cause and cardiovascular mortality except for running frequency of 6 times/wk or more (*P*=.11) and speed of less than 6.0 mph (*P*=.10) for cardiovascular mortality. MET = metabolic equivalent. Reproduced with permission from *J Am Coll Cardiol*.[11]

walking 1.8 to 3.6 MET-h/d lowered all-cause mortality (−29%), CVD mortality (−34%), cerebrovascular mortality (−55%), and heart failure mortality (−51%), as did running or walking 3.6 MET-h/d or more (−22%, −36%, −47%, and −45%, respectively).[34] All results remain significant when adjusted for BMI.

Of the 2160 participants who reported using medications for T2DM, 331 died during the 9.8-year follow-up.[35] Meeting the national exercise recommendations was not associated with lower all-cause mortality, whereas exceeding those recommendations was associated with 36% reduction in death. Greater levels of exercise (in MET hours per day) was associated with a 40% lower risk of chronic kidney disease−related death, 31% lower risk of sepsis-related death, and 31% lower risk of death from pneumonia.[35] In fact, running or walking 1.8 MET-h/d or more was associated with a 57% reduction in CVD-related mortality.

In the Copenhagen City Heart Study, jogging habits were recorded in 17,589 healthy men and women and 1878 joggers (1116 men and 762 women) and were compared with nonjoggers during a 35-year maximal follow-up, in which 122 deaths were recorded among joggers compared with 10,158 deaths among nonjoggers.[13] After

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adjustment for multiple other variables, joggers had a 44% reduction in all-cause mortality compared with nonjoggers, which was associated with an average increase in survival of 6.0 years in men and 5.6 years in women. A more recent analysis of this cohort assessing doses of jogging and long-term mortality revealed that maximal reduction in long-term mortality occurred at lower doses of jogging.[14] In fact, compared with sedentary nonjoggers, 1 to 2.4 hours of jogging per week was associated with the lowest mortality (71% reduction in death). This study suggests that the optimal frequency of jogging was 2 to 3 times/wk (68% reduction in mortality) or 1 time/wk or less (71% reduction in mortality). When joggers were divided into groups performing light, moderate, and strenuous jogging, a marked mortality reduction was noted in groups performing light jogging and moderate jogging, whereas groups performing strenuous jogging appeared to lose their mortality reduction (hazard ratio, 1.97; 95% CI, 0.48-8.14), suggesting a U-shaped relationship between jogging dose and subsequent mortality (Figure 1).[14] However, some of us (D.-c.L., C.J.L.) have questioned the value of drawing conclusions from these data because of a smaller sample size and deaths among the group performing strenuous jogging.[12] Nevertheless, these results certainly support the observation that maximal protection against mortality appears to occur at relatively low doses of jogging.

Several of us have recently analyzed 55,000 individuals (13,000 runners) from the ACLS database during nearly 15-year follow-up to assess the impact of running on CVD and all-cause mortality.[11] Compared with nonrunners, runners had a reduction in all-cause and CVD mortality of 30% and 45%, respectively, with an average increase in survival of 3.0 and 4.1 years for all-cause and CVD-related survival, respectively, after adjusting for lifestyle factors (eg, smoking and obesity) and medical conditions (eg, HTN and T2DM). Persistent runners appeared to receive the full benefit from mortality reduction, whereas those who started running but stopped or those who were not running at baseline but subsequently started running appeared to receive nearly half of the benefit received from CVD and all-cause mortality reduction. These results are impressive, though perhaps not surprising when considered in the context of the data outlined in previous sections, showing myriad health benefits of running.

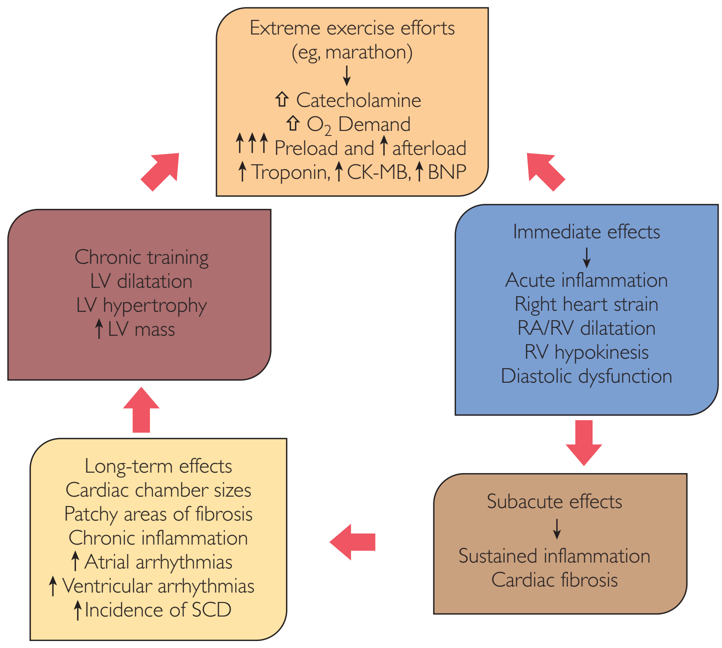

FIGURE 4. Proposed pathogenesis of cardiomyopathy in endurance athletes. BNP = B-type natriuretic peptide; CK-MB = creatine kinase MB; LV = left ventricular; RA = right atrial; RV = right ventricular; SCD = sudden cardiac death. Reproduced with permission from *Mayo Clin Proc.*[7]

However, when assessing doses of running, somewhat surprising results were found. Runners generally had considerably higher levels of CRF than did nonrunners, and moreover, CRF levels in runners progressively increased with increasing doses of running (Figure 2).[11] Most evidence indicates better survival with estimated MET levels greater than 10,[23-25] although some evidence indicates progressively better survival with even higher CRF levels.[45] When 13,000 runners were divided into quintiles of running doses (miles per week, times per week, minutes per week, and speed), no significant differences in the benefits were noted for any of the running groups. In fact, runners in quintile 1 (eg, <6 miles/wk, 1-2 times/wk, <51 min/wk, <6 mph) received the full benefits from running with regard to reduction in CVD and all-cause mortality (Figure 3).[11] These results suggest that maximal benefits of running occur at quite modest jogging doses and that runners in quintile 1 have almost similar benefits of running compared with those in quintile 2 to quintile 4 and have a slight, nonstatistically significant

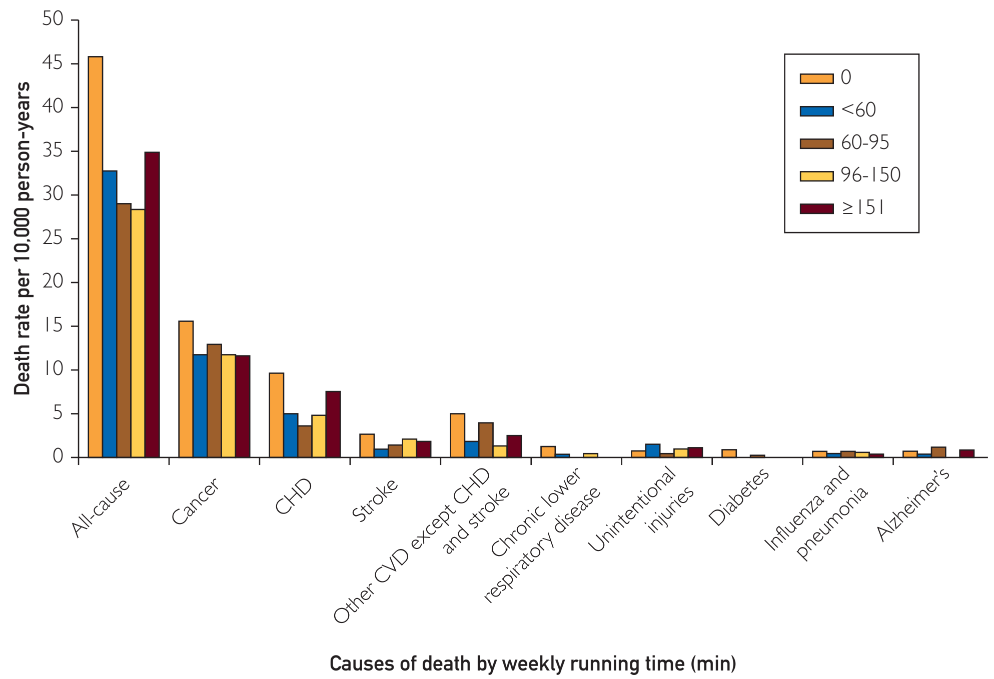

FIGURE 5. Participants were classified into 5 groups: nonrunners and 4 quartiles of average weekly running time (in minutes). Death rates were adjusted for baseline age, sex, and examination year, and causes of death were divided into all-cause, cancer, CHD, stroke, other CVD, chronic respiratory disease, unintentional injuries, diabetes, influenza and pneumonia, and Alzheimer disease. CHD = coronary heart disease; CVD = cardiovascular disease. Reproduced with permission from *J Am Coll Cardiol*.[12]

trend toward greater benefit compared with those in quintile 5. However, in contrast to the results of the Copenhagen City Heart Study,[14] our results, from a larger sample with much better statistical power, indicated that runners with high doses of running in quintile 5 still had significantly better CVD and all-cause survival compared with nonrunners.[11] However, these higher doses of running were not necessary to achieve maximal reduction in CVD and all-cause mortality.[11-14]

POTENTIAL CARDIOTOXICITY OF HIGH DOSES OF AEROBIC EXERCISE, INCLUDING RUNNING

Although higher levels of aerobic PA and ET, including running, are associated with numerous health benefits, including protection against CVD and all-cause mortality, as compared with a sedentary lifestyle, there still may be potential adverse effects from high doses of running and other forms of EET,[7-9] such as marathons, ultramarathons, Iron Man distance triathlons, and long, high-intensity bicycle rides (Figure 4).[7] The potential adverse effects of aerobic ET have been debated, with several reports focusing on the potential cardiotoxicity[7-9,46] whereas others have cautioned that the data for cardiotoxicity may not be powerful enough to overly frighten athletes who participate in EET.[47,48]

We have previously reviewed the potential adverse effects of EET.[7-9] In animals, high levels of ET have been associated with atrial and ventricular enlargement, fibrosis, and propensity for high-grade ventricular arrhythmias, which reverse after detraining.[7-9,49] In humans, marathon running has been associated with an increase in cardiac troponin and brain natriuretic peptide levels, which are markers of myocardial necrosis and heart failure, respectively, in approximately one-third of the competitors.[7-9] In addition, marathon running has been associated with a marked increase in atrial size and dilation of the ventricular chambers, especially the right ventricle, with a reduction in function, especially of the right ventricle and the ventricular septum.[7-9,50] Fortunately, all these abnormalities seem to resolve within the first 1 to 3 days after

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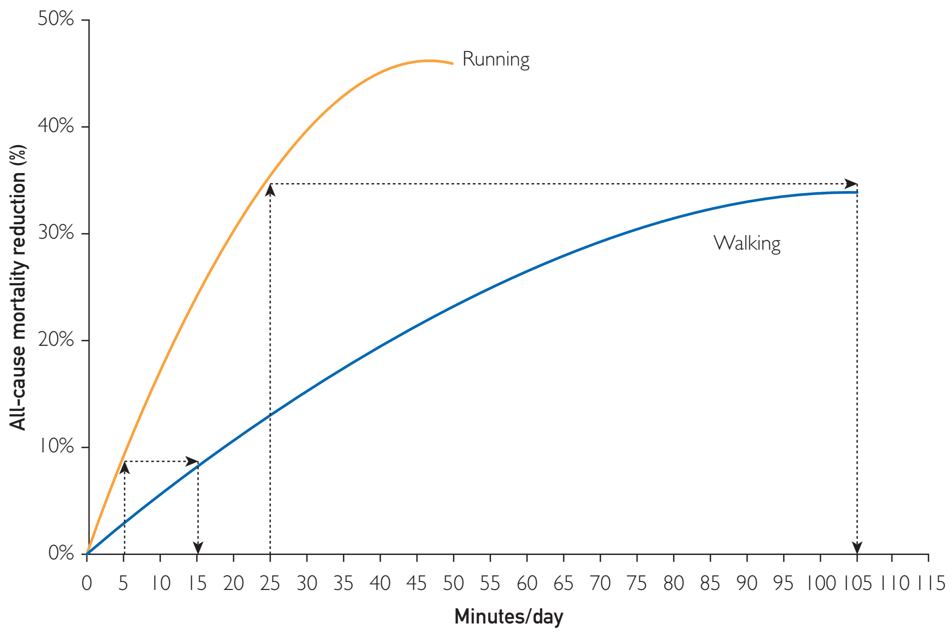

FIGURE 6. A 5-minute run generates the same benefits as a 15-minute walk, and a 25-minute run is equivalent to a 105-minute walk. Reproduced with permission from *J Am Coll Cardiol*.[57]

the marathon and certainly in the next week, without obvious permanent adverse effects on most marathon participants. In a recent major study of marathon runners performed in the United States during a 10-year period, deaths were noted in only 0.54 per 100,000 participants.[7-9,16] Some have criticized these data, suggesting that the statistics were contaminated by half-marathoners and may account for deaths only in the marathon and immediately after (but not within the 1-3 days after the event) and that the true mortality may be 2 to 3 times higher than this estimate; nevertheless, the overall mortality in marathons appears relatively low.[7-9,47,48]

In addition, recent studies suggest that marathon runners, despite having lower overall CHD risk factors, may actually have a higher risk of CHD, especially at higher doses than at lower doses (Figure 5),[12] including higher levels of coronary artery calcium and more plaque on intravascular ultrasound.[7-9,51,52] Williams and Thompson[43] also recently reported on 2400 individuals with a history of MI. In this group, higher levels of exercise (up to ~7.2 MET-h/d) were associated with a progressive reduction in CVD mortality, followed by a sharp increase in CVD-related mortality. Although individuals with these high doses of exercise (equivalent to 30 miles/wk of running or 46 miles/wk of walking) did not have higher CVD mortality than did nonexercisers, this group appeared to lose most of their protection against CVD-related mortality noted at the more moderate ET doses, thus increasing the possibility that high doses of aerobic exercise may not be ideal for individuals with CHD with a history of MI. The potential cardiotoxicity of EET is discussed further below.

Furthermore, many studies and meta-analyses have reported a U-shaped relationship between aerobic PA and ET and risk of atrial fibrillation (AF), with a reduced risk of AF in those with low-moderate ET volume as compared with sedentary controls whereas those with high ET volume appeared to have an increased risk of AF.[53,54] Recently, we reviewed several studies and meta-analyses reporting an increased risk of AF associated with high-intensity exercise,[53,54] whereas one meta-analysis did not come to this conclusion.[55]

EXERCISE AND RUNNING DOSES RECOMMENDATIONS

According to a set of data, there are numerous benefits of running. Even in

1993, Haskell et al[56] reported that in 11 ultradistance runners, the dilating capacity of the epicardial arteries was markedly increased and correlated positively with their CRF and negatively with their adiposity, reduced heart rate, and plasma lipoproteins, and these benefits have now been considerably extended with the evidence discussed above. However, the current recommendation of 150 min/wk of moderate or 75 min/wk of vigorous aerobic PA by the US PA guidelines seems to be sound,[10] realizing that with running, which would be considered a vigorous aerobic PA, significant, and possibly maximal, health benefits may occur at levels well below this recommendation,[11-15,57] supporting the idea that some PA in the form of running is considerably better than no PA. In addition and specifically with running, as reviewed above, maximal benefits appear to occur at quite low doses.[11-15] In general, running for 5 minutes may equal approximately 15 minutes of walking and 25 minutes of running may equal approximately 105 minutes of walking, suggesting that 3 to 4 times the duration of walking is needed to achieve the same benefits as of running (Figure 6).[57] Likewise, in the Copenhagen City Heart Study,[13,14] ACLS,[11,12] and Wen analyses,[15,57] maximal benefits of running occur at low levels, certainly maximizing at 40 min/d or less.

Therefore, EET is not needed to maximize protection against CVD and all-cause mortality. In addition, EET at levels of running well above 40 min/d is associated with some risks, although these risks appear relatively low.[7-9] Although many individuals want to participate in sporting events that require EET, such as marathons and triathlons, for various reasons (eg, competition, fun, psychological benefits, weight loss, stress relief, fitness improvement, and challenge) that extend well beyond merely health effects, they should realize that these EET events and the training involved in participating in these events may be associated with some health risks, albeit relatively low. Because the risks associated with EET, including long running distances, are quite low, we must be careful to not overly frighten these athletes or to exaggerate health risks.[47,48] Clearly, most participants in these events are required to be quite healthy overall with high levels of CRF so as to consider these events in the first place. Although data on how to handle participants in EET are not readily available, we believe that in middle-aged athletes, particularly those with CHD risk factors, coronary artery calcium scanning, exercise stress testing, low-dose aspirin therapy, and statin therapy could be considered, as recently reviewed.[58]

CONCLUSION

Substantial data indicate the marked benefits of vigorous aerobic PA and CRF on subsequent health. Substantial evidence indicates that running, a common form of vigorous aerobic PA, has numerous health benefits, with some evidence indicating that benefits apparently maximizing at quite low doses of running. Although there may be some negative health consequences of EET, such as prolonged running (eg, marathons and triathlons), which are relatively small, the overall benefits of running far outweigh the risk for most individuals and are associated with considerable protection against chronic diseases and CVD and all-cause mortality.

Abbreviations and Acronyms: **ACLS** = Aerobics Center Longitudinal Study; **AF** = atrial fibrillation; **BMI** = body mass index; **CHD** = coronary heart disease; **CRF** = cardiorespiratory fitness; **CVA** = cerebrovascular accident; **CVD** = cardiovascular disease; **DLP** = dyslipidemia; **EET** = extreme exercise training; **ET** = exercise training; **HTN** = hypertension; **MET** = metabolic equivalent; **MI** = myocardial infarction; **OA** = osteoarthritis; **PA** = physical activity; **T2DM** = type 2 diabetes mellitus

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