Systematic Review/Meta-analysis

The Acute Risks of Exercise in Apparently Healthy Adults and Relevance for Prevention of Cardiovascular Events

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ABSTRACT

Background: Increased physical activity (PA) is associated with improved quality of life and reductions in cardiovascular (CV) morbidity and all-cause mortality in the general population in a dose-response manner. However, PA acutely increases the risk of adverse CV event or sudden cardiac death (SCD) above levels expected at rest. We review the likelihood of adverse CV events related to exercise in apparently healthy adults and strategies for prevention, and contextualize our understanding of the long-term risk reduction conferred from PA.

Methods: A systematic review of the literature was performed using electronic databases; additional hand-picked relevant articles from reference lists and additional sources were included after the search.

Results: The incidence of adverse CV events in adults is extremely low during and immediately after PA of varying types and intensities and is significantly lower in those with long-standing PA experience. The risk of SCD and nonfatal events during and immediately after PA remains extremely low (well below 0.01 per 10,000 participant hours);

The cardiovascular (CV) health benefits conferred by increased habitual physical activity (PA) are now widely accepted. 1,2 Current evidence supports a dose-response pattern, largely indicating that optimum risk reduction is achieved with vigorous PA. 3-6 Exercise intensity of various PA types is typically quantified using metabolic equivalents (METS), or the rate at which the body expends energy above rest (1 MET = 3.5 mL of oxygen per kilogram of body mass per minute), with vigorous exercise considered to be greater than 6 METs, as outlined in the compendium of physical activities published by the American College of Sports Medicine. 7 However, although such classification is applicable to the general untrained population, those engaged in regular vigorous exercise commonly perform exercise well above 8 METs, with trained athletes often exceeding an intensity of 12-15 METs for a sustained time period. 7,8 Nonetheless, early observations suggested a linear relationship between increasing energy expenditure and low mortality rates through vigorous PA of at least 4187 J/wk (1000 kcal/wk), but optimally closer to 8374 J/wk (2000 kcal/wk) yield the greatest risk reductions for CV disease (CVD) mortality. 4,6 More recent data largely confirm these findings but show that numerous health benefits at the population level might be conferred from lesser volumes of PA. Decreased all-cause and CV mortality rates have been observed with as little as 30-59 min/wk of jogging, 9 as well as either an attenuation or threshold effect 10,11 or a loss of cardioprotection at very high levels of PA. 12,13

Notwithstanding the health benefits of moderate to intense PA, adverse CV events, particularly sudden cardiac death (SCD) during or immediately after exercise, pose concerns for participants and health practitioners alike. Such events are accompanied by considerable media attention because victims are performing the very activity purported to

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METHODS : Nous avons réalisé une revue systématique de la littérature à partir des banques de données électroniques. Nous avons inclus des articles pertinents additionnels triés sur le volet provenant de listes de référence et de sources complémentaires après la recherche.
increasing age and PA intensity are associated with greater risk. In most cases of exercise-related SCD, occult CV disease is present and SCD is typically the first clinical event.

**Conclusions**: Exercise acutely increases the risk of adverse CV events, with greater risk associated with vigorous intensity. The risks of an adverse CV event during and immediately after exercise are outweighed by the health benefits of vigorous exercise performed regularly. A key challenge remains the identification of occult structural heart disease and inheritable conditions that increase the chances of lethal arrhythmias during exercise.

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**Pathophysiology of Exercise-Induced Adverse CV Events**

The pathophysiology underlying exercise-induced SCD has been well described and theorized. In health, adequate coronary blood flow reserve and normal cardiac electrical activity occur during vigorous exercise. However, in the presence of coronary artery disease, the production of malignant substrates during or immediately after exercise stress might trigger a cascade of physiological events precipitating an adverse event (Fig. 1). Most exercise-related SCD cases in individuals older than 30-35 years of age are secondary to acute complications of atherosclerosis, which is associated with >80% of exercise-related SCD in individuals older than 35 years of age, and >95% of cases when the age exceeds 40 years. Autopsy findings generally indicate acute myocardial infarction, but evidence of coronary thrombosis is not always identifiable. Exercise stress is considered to be a risk factor for acute and vulnerable atherosclerotic plaque, likely by accelerating the fissing of fragile, nonocclusive plaque secondary to mechanisms that remain unclear. Altered geometric and hemodynamic states of epicardial arteries (e.g., increased shear stress or geometry), might in turn lead to plaque disruption. Plaque rupture might also be spontaneously induced through increased fibrinolytic activity triggered by a prothrombotic state induced by vigorous, but not moderate exercise.

The identification of disease presence (or severity) remains a key limiting factor in the prevention of adverse outcomes because previous symptoms are absent in most cases of exercise-related SCD. This is also true for preparticipation screening, which might mitigate some, but not all cases of SCD. In SCD cases involving younger individuals (e.g,
younger than 30-35 years), disorders of myocardial structure and/or conduction remain the common diagnoses, including inherited genetic diseases that account for most pathological findings in cases of SCD (including hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, Brugada disease, and Marfan syndrome). Disturbances in electrical conduction might be a ‘concealed’ cause of death in young and older athletes despite normal histology because conduction systems are rarely examined or fail to show abnormalities upon inspection. Less common congenital conditions include anomalous coronary arteries, which are linked to SCD in young and older athletes.

Epidemiological Perspectives: Dose-Response of Chronic PA and Risk Reduction

The risks of exercise should be considered in the context of long-term health benefits, CV, and all-cause mortality risk reduction. More than 30 meta-analyses, and large retrospective and prospective studies unequivocally support the health benefits of low to vigorous PA. These data and have led to current recommendations for weekly PA, ranging from 75 minutes of vigorous up to 150 minutes per week of moderate to vigorous PA. Although many studies show a linear dose-response effect favouring more vigorous PA, emerging evidence suggests the dose-response effect (exercise dose vs risk reduction) might not be linear and little if any additional health or risk-reduction benefits might come from high-volume, high-intensity exercise (eg, marathon running). For example, when PA involves higher levels of either duration, frequency, intensity, or a combination of these factors, some studies show a point of diminishing return or attenuation effect (‘reverse J’ relationship) for risk reduction, and others report a loss of cardioprotective or all-cause mortality benefit (showing a ‘U’ shaped relationship) when exercise volume exceeds a certain threshold. However, these latter studies are limited by a number of important factors, including wide, overlapping confidence limits between groups, small higher-volume exercise groups with low death rates, or a relatively high prevalence of smoking in highly active ‘exercisers.’ The studies with large, equally populated quintiles of exercise show significant benefits from moderate to high levels of PA, with an attenuation effect confirming benefits at moderate, but no further benefits in joggers reporting higher MET min/wk, duration, frequency, and distance; these data from runners indicate that ‘more is not better.’ Moreover, ‘excessive’ endurance exercise has indeed been linked to adverse findings of uncertain etiology, including transient cardiac dysfunction and increased levels of biomarkers of injury after prolonged endurance competition. Furthermore, an increased risk of arrhythmias, particularly atrial fibrillation in longstanding middle-aged endurance athletes has given rise to the concern that for some, ‘more might be worse.’ Further research is required to determine the phenotypic and/or genotypic factors that predispose some, but not all individuals who perform regular ‘excessive’ exercise. Despite these observations, even elite endurance athletes who perform extremely high exercise volumes have lower mortality rates and improved longevity compared with the general population.

Collectively, these observations have complicated the understanding of the risk-benefit relationship between PA and morbidity or mortality risks. However, there is clear evidence of various health benefits and risk reduction conferred from
vigor exercise that outweighs the risks of exercise in most of the population.

**Acute risks and habitual PA**

Although the risk of CV events is increased during acute exercise, long-term compliance with a vigorous exercise regimen significantly decreases this risk. This has been reported in retrospective and prospective studies, the latter showing more than a fivefold reduction in risk of myocardial infarction if exercise occurs > 4-5 d/wk, with a diminishing effect with less weekly exercise. Even infrequent participants or ‘weekend warriors’ of PA (1-2 times per week), have a lower level of acute risk. Data from the Nurses’ Health study indicates the transient increased risk was virtually eliminated in those who reported more than 2 hours of moderate to vigorous PA per week. Exercise capacity might also be an independent and more powerful predictor of death in asymptomatic women compared with men. A 17% reduction in mortality rate was observed per MET increase in exercise capacity, adjusted for the Framingham Risk Score, compared with a 12% risk reduction for a similar increase in exercise capacity in men. These data suggest that higher fitness levels and in particular, ongoing participation in vigorous PA greatly reduces the risk of CV events during acute exercise and in the long-term.

**Preparticipation Screening in Middle-Aged Adults: Does It Work?**

**Preparticipation questionnaires**

Various questionnaires have been developed to identify an increased risk of CV events during exercise, including the modified American Heart Association/American College of Sports Medicine Facility Preparticipation Screening Questionnaire, which provide a basis for risk stratification and addresses a broader range of diseases that might complicate the response to exercise. The Physical Activity Readiness Questionnaire (PAR-Q) has been used extensively as a screening instrument. However, recent work has highlighted that the original American College of Sports Medicine risk stratification and PAR-Q instruments unduly burdened health care infrastructure and posed an unnecessary barrier to PA. This is because an overwhelming percentage of adults (older than 45 years of age) would be required to undergo a physician consultation and/or a graded exercise stress test before exercise participation simply because of ‘age,’ prescription medication use, or presence of medical conditions, who in fact would be recommended for exercise. The new PAR-Q for Everyone and electronic Physical Activity Readiness Medical Examination were recently developed using an evidence-based approach (www.eparmedx.com), greatly reducing the barrier to PA participation for most adults. Subsequently, the American College of Sports Medicine has since revised their guidelines and risk algorithm.

**Value of exercise testing**

The occult nature of coronary disease remains a primary challenge in identifying an increased risk with vigorous exercise. Stress testing using electrocardiogram (ECG) alone or ideally cardiac imaging modalities (perfusion scanning or echocardiography) attempts to identify lesions of sufficient severity to cause objective ischemia. However, the risk of SCD during or after exercise is not limited to this group, because nonocclusive lesions might just as likely precipitate an acute coronary event through coronary vasospasm or spontaneous plaque fissuring, causing ischemia and serious arrhythmia during subsequent exercise. Measures of coronary artery calcium scores is an emerging alternative in assessment of atherosclerotic burden and higher coronary artery calcium scores have been linked to nonexercise, long-term CV event rates in marathoners, yet further evidence supporting its validity and role in relation to exercise risk is required. In addition, the pretest likelihood of coronary artery disease and in many cases, the inability of an individual to reach maximal effort during exercise testing, yields a low sensitivity for detecting changes in the ST segment, thereby limiting the efficacy of stress testing in low-risk patients. Another limitation is the wide range of specificity and sensitivity across cohorts and diagnostic techniques, which in turn is dependent on the extent of disease or inherent predisposition for false positive results, such as those seen in women. The greater likelihood of false positive test results might lead to spuriously labelling of the individual as ‘higher risk,’ which in turn might prompt unnecessary invasive diagnostic procedures, anxiety, and possibly poorer future health. This is also true for middle-aged recreational and elite athletes in whom a higher prevalence of abnormal ECGs are observed, many of which are benign or have uncertain clinical relevance, further undermining the clinical utility of stress testing as an appropriate method to rule out coronary artery disease, especially in the longstanding, aging exerciser.

Because equivocal or false positive results are more likely when the absolute risks of exercise are low, stress testing with electrocardiographic monitoring before initiating exercise is no longer recommended for low- to moderate-risk adults (eg, ≤ 2 risk factors for CVD and/or diagnosed chronic disease). Consequently, ascertaining a comprehensive, overall risk profile might help to identify heightened risk for coronary disease, but stress testing alone might not identify those at acute risk for SCD. Current guidelines call for preparticipation exercise testing only in high-risk individuals (known CV, metabolic, pulmonary, or renal disease). However, further consideration should be given for those for whom concerns of increased risk (by clustering of certain risk factors) can be justified by a health professional or the patient/participant has concerns about safely participating in vigorous exercise. Nonetheless, maximal and submaximal exercise testing remains a valuable and low-risk tool for more precise exercise prescription.

**Presence of Signs and Symptoms**

Exercise testing of young athletes has become common practice in professional sports, but it is rarely performed in amateur athletes or the general population in North America except when CVD is suspected. Exercise-related abnormalities in the athlete are beyond the scope of this review, but some mention is warranted as it relates to the exercising adult. The significance of numerous 12-lead ECG ‘abnormalities,’
particularly in endurance athletes, remains to be determined and the thresholds defining 'normal' have recently changed. Notably, the European Society of Cardiology provides guidelines for interpretation of the athletic ECG and the 'Seattle Criteria' have further refined the stratification process, thereby significantly decreasing the number of false positive diagnoses.

Although the presence of exercise-induced ventricular arrhythmias in young or middle-aged athletes, or the sedentary population during exercise testing has uncertain prognostic value, frequent ectopy has yet to be linked with increased risk except in those at high risk of coronary ischemia or existing myocardial damage. However, no clear data on adverse events during exercise testing has uncertain prognostic value, frequent ectopy has yet to be linked with increased risk except in those at high risk of coronary ischemia or existing myocardial damage. However, no clear data on adverse events except in those at high risk of coronary ischemia or existing myocardial damage. However, no clear data on adverse events.

In reality, many early hospital record studies were not supported by autopsy data to confirm a cause of death. Census data have attributed > 80% of deaths during or immediately after exercise (in only 81 men) to atherosclerotic disease, with an incidence of death for men and women older than 30 years of age as 4.46 and 0.05 per 100,000, respectively. The widely cited report of Thompson et al. on Rhode Island joggers reported 1 death per 396,000 person-hours of jogging, on the basis of 1 death report from 7620 regular joggers, suggesting that acute exercise increases the risk of an acute coronary event by 7 times. These data are in agreement with another report that showed a gradient of risk according to the amount of PA performed weekly: those with the highest reports of habitual PA (≥ 140 min/wk) had a fivefold increase in the risk of cardiac arrest during vigorous PA vs those with the least (1-19 min/wk) who had a 56-fold greater relative risk. Similar but less dramatic trends have been reported, with a relative risk of 6.3 for adverse CV events for those exercising < 4 times per week, and only 1.3 for those exercising > 4 times per week. These data suggest that adverse CV event risk might be increased during acute exercise, but overall risk might be decreased with increasing levels of habitual exercise.

Retrospective multicentre data from fitness facilities report low rates of adverse CV events. The advantage of these studies is the massive cumulative hours of exposure to exercise. A 5-year retrospective analysis of 48 fitness facilities (totaling 22,726,000 participant hours) reported an incidence rate for nonfatal and fatal events of 1/1,124,200 person-hours of participation, respectively (0.13 and 0.16 complications per year). Even lower rates were reported from YMCA facilities (1/2,897,057 person-hours of PA).

Prospective studies

The small number of prospective studies that tracked CV adverse events reported higher event rates ranging from 0.3 to 2.7 events per 10,000 person-hours of exercise (across all age groups) for men and 0.6-6.0 events per 10,000 person-hours for women. Higher values for women were due to the smaller sample size, but when normalized to similar exercise frequencies and duration for a 1-year period, the incidence of exercise-induced SCD in women is similar to other reports, typically 5%-10% of that seen in men. A large study examined acute risks of vigorous exercise during a 12-year follow-up of 21,248 adults. In total, 122 cases of sudden death were reported, yielding a relative risk during and up to 30 minutes after vigorous exertion, of 16.9 (95% confidence interval, 10.5-27.0). This is equivalent to an absolute risk of 1 SCD per 1.51
more importantly, the shifting of the age group. The fastest sporting event risk is of particular interest because of the trend in Mass participation endurance events. Mass participation sporting event risk is of particular interest because of the trend of increasing participation rates of road races, including marathons (with an increase of > 12-fold since 1976) and more importantly, the shifting of the age group. The fastest growing cohort of these events are those older than 40 years of age (as of 2014) with 40% of all participants older than 40 years of age, compared with 23% in 1980. Similar data now exist for ultramarathon participation as well, with greater participation overall, and greater representation of older athletes. This trend is expected to continue as the population ages and the baby boom age group continues to engage in this form of activity.

Media reports of fatal cardiac events at various marathons in Canada and the United States have heightened the concern and have led to a number of retrospective analyses of risk.100-103 Recent data indicate the risks of a fatal CV event during marathon or half marathon events is extremely low, with reported incidence rates of SCD being as high as 1/50,000 and as low as 0.54/100,000 to 1/200,000, with higher rates for men vs women (0.90/100,000 and 0.16/100,000, respectively). The most recently reported data indicate an incidence rate for cardiac arrest and sudden death of 1/184,000 and 1/259,000, respectively. The risk is greater for longer-distance events (eg, full vs half marathons), and most adverse CV events occur near the completion or immediately after the race. This is possibly because of the progressive effects of dehydration and electrolyte disturbances, increases in levels of catecholamines, and increased exercise intensity often observed in the final pursuit to the finish line. Collectively, these data are from extremely large sample sizes, often exceeding 30,000-50,000 participants per event. Even if the relative risk for coronary disease is conservatively estimated to be 20% less than average in these participants, a sizable number of participants would still have some degree of coronary disease, yet the incidence of SCD remains extremely low. In fact, a recent study indicated that the prevalence of atherosclerosis in marathon-running men older than 45 years is 50%, yet only a minority have significant lesions of clinical relevance. The increasing incidence of atherosclerosis in this cohort appears to be related to age, independent of marathon-running history.

Despite these low incidence rates, readily available defibrillators are essential elements of medical preparedness during well organized marathon and shorter events because of the observations of improved survival after prompt use of automatic external defibrillators in marathons and in particular, the last 6 km in which most cardiac events occur.

Resistance exercise and alternative forms of PA

There are few data on specific adverse responses to PA other than traditional aerobic exercise. The CV risks of resistance training appear to be relatively low, however, data from relatively small studies are insufficient to provide accurate estimates of risk across the general population. Appropriate techniques, including the avoidance of theValsalva manoeuvre during lifting, can mitigate blood pressure responses to that seen with aerobic exercise, providing the effort is below the maximal lift capacity (eg, 1-repetition maximum). Interestingly, there is some evidence suggesting that intense resistance training reduces the compliance of central arteries, but this finding is not universal. Arterial stiffening has been directly linked to an increased pulsatile load, organ damage, morbidity, and mortality, yet the effects of a less compliant arterial tree and CV event risk during PA are unclear. Limited data suggest that the assessment of maximal strength or circuit training (eg, rotating through stations involving mixed exercise combining strength and aerobic exercise) is safe, with no adverse CV events reported from these studies.

Cardiovascular risk performing recreational activities such as mild (< 3 METs) to vigorous (> 6 METs) hiking and snow skiing are more difficult to interpret because these are typically reported as days of skiing, hiking, etc, with low incidence rates reported (1/319,000 days, nonfatal events; 1/980,000 days, fatal events) in individuals older than 40 years of age. Very low incidence rates are reported for hiking (1 death per 5,000,000 hiking hours) and downhill skiing (1/630,000 downhill skiing hours) in men older than the age of 34 years. It is likely that exposure to high altitude and the associated reduction in the partial pressure of oxygen might compromise myocardial oxygen supply in the presence of a flow-limiting lesion. Collectively, these studies suggest a low incidence rate of CV events for winter and alpine sports.

Are Women Protected From SCD During Exercise?

Women have a considerably lower incidence rate of exercise-related SCD, likely because of the delay seen in coronary heart disease and until recently, the historically lower participation rates in vigorous PA. In one of the few prospective studies on PA in women, the ongoing Nurses’ Health Study examined 84,888 women and only 3.1% of the cohort died during moderate or vigorous activity, including activities from yard work to vigorous exercise. The risk of cardiac sudden death in women associated with moderate or vigorous exercise of 1 per 36.5 million hours, is much less than those reported previously in a much smaller study, and SCD rates during marathons or half marathons are < 25% that of men. Since the late 1990s, there has been a 40% increase in female participation rates for mass participation events in general and the marathon in particular. During this time, the gap between men and women for either sudden cardiac arrest or SCD rates during marathons has actually widened, reflecting the greater disease burden in the male cohort.
Knowledge Gaps and Recommendations

Despite the overwhelming evidence confirming that adverse CV events during vigorous PA are rare, the occurrence of such events is tragic and often ironic for individuals engaged in the very activity known to reduce risk and promote health. Such events are frequently the first clinical manifestation of disease, yet remain a rare occurrence and efforts to promote vigorous PA should not be curtailed, but rather the reverse and the promotion of PA for less active individuals should involve sensible and gradual progression toward moderate and vigorous levels of intensity. The identification of vulnerable lesions and the triggers of their disruption requires further research. We also lack sufficient data on numerous types of vigorous activity performed by mid-aged adults that occurs outside organized leagues or mass participation events, such as pick-up hockey and snow-shoveling. Although anecdotal reports of fatal and nonfatal events for such activities are not uncommon, objective data are lacking. It is time to establish a registry to systematically record, with appropriate detail, all adverse CV events related to PA. Finally, we need to more clearly distinguish between the low mortality risks of performing PA vs the poorly understood phenomena of increased prevalence of exercise-related arrhythmias, which might not necessarily confer a shortened lifespan, but might provoke undesired complications with uncertain consequences.

Conclusions

PA increases the risk of fatal and nonfatal CV adverse events significantly relative to the resting state. This increased risk is directly linked to increasing exercise intensity and age. Most cases of fatal CV events occur without prodrome, suggesting that identification of occult and vulnerable CVD remains the key challenge in reducing exercise-related adverse CV events. A history of regular PA, particularly when performed at a vigorous intensity, significantly reduces risk of each exercise session. Despite the increased risk of a CV event during acute exercise, the benefits of regular vigorous exercise for CV risk reduction outweigh the risks associated with sedentary behaviour for most of the population.

Funding Sources

J.M. Goodman receives operating grant support from the Canadian Institutes of Health Research. L. Banks is funded by a Canadian Institutes of Health Research Post-Doctoral Research Fellowship.

Disclosures

The authors have no conflicts of interest to disclose.

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