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MINIREVIEWS

Physical activity in primary and secondary prevention of cardiovascular disease: Overview updated

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Abstract

Although the observed progress in the cardiovascular disease treatment, the incidence of new and recurrent coronary artery disease remains elevated and constitutes the leading cause of death in the developed countries. Three-quarters of deaths due to cardiovascular diseases could be prevented with adequate changes in lifestyle, including increased daily physical activity. New evidence confirms that there is an inverse dose-response relationship between physical activity and cardiovascular disease and mortality risk. However, participation in moderate to vigorous physical activity may not fully attenuate the independent effect of sedentary activities on increased risk for cardiovascular diseases. Physical activity also plays an important role in secondary prevention of cardiovascular diseases by reducing the impact of the disease, slowing its progress and preventing recurrence. Nonetheless, most of eligible cardiovascular patients still do not benefit from secondary prevention/cardiac rehabilitation programs. The present review draws attention to the importance of physical activity in the primary and secondary prevention of cardiovascular diseases. It also addresses the mechanisms by which physical activity and regular exercise can improve cardiovascular health and reduce the burden of the disease.

Key words: Physical activity; Primary prevention; Secondary prevention; Cardiovascular disease; Health care evaluation mechanisms

Core tip: This review describes the benefits of physical activity in primary and secondary prevention of cardiovascular disease. Physical inactivity is related to high blood cholesterol and accumulation of visceral fat, accompanied by low-grade vascular inflammation, which in turn is associated with insulin resistance and atherosclerosis leading to the development of coronary artery disease. In contrast, physical activity decreases vascular inflammation, and improves endothelial function and coronary circulation, preventing myocardial ischemia. Health professionals and policy makers in public health should align strategies to increase participation in physical activity.

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INTRODUCTION

Notable progresses have been observed in the treatment of cardiovascular disease. Hence, cardiovascular mortality faced a progressive decline in the past two decades. Despite these progresses, incidence of new and recurrent coronary artery disease (CAD) remains elevated[1] and constitutes the leading cause of death in the developed countries[2]. This is expected to increase health care costs, increase work disability and reduce quality of life[3].

Development of cardiovascular diseases is associated with lifestyle behaviours, such as smoking, unhealthy diet, physical inactivity[4] and sedentary behaviour[5]. Physical inactivity is defined as not meeting 150 min weekly practice of moderate physical activity or 75 min of vigorous physical activity. Regardless of the physical activity recommendations, the accumulation of sedentary behaviour, characterized by a series of activities with low energy expenditure ($\leqslant$ 1.5 metabolic equivalents, *e.g.*, watching television, using the computer, playing video game or riding in a car) throughout the day seems to increase the risk of degenerative chronic diseases and death risk[5]. Over three-quarters of deaths due to cardiovascular diseases could be prevented with adequate changes in lifestyle[4]. Indeed, the adoption of healthy life habits such as increasing physical activity and decreasing sedentary behaviours are able to decrease the risk of type 2 diabetes, stroke, cardiac events and cardiovascular disease[5] improving the quality of life and decreasing risk of death[6]. Several studies have addressed the importance of increasing physical activity levels as a public health intervention[7]. However, even though it is an important factor in primary and secondary prevention[8], the levels of compliance with the physical activity recommendations are still far from desirable[9]. Therefore, enhancing physical activity is still considered a challenge to public health.

The present review draws attention to the importance of physical activity in the primary and secondary prevention of cardiovascular diseases. It also addresses the mechanisms by which physical activity and regular exercise can improve cardiovascular health and reduce the burden of the disease.

PHYSICAL (IN)ACTIVITY AND SEDENTARY BEHAVIOURS

Physical inactivity is the fourth leading risk factor for non-communicable diseases[10]. It is independently responsible for 12.2% of the global burden of acute myocardial infarction[7] as well as 6% of deaths that occur worldwide[9]. Due to its elevated prevalence, physical inactivity is responsible for almost as many deaths as smoking[11,12]. It is estimated to cause 5.3 million deaths worldwide[13] and to increase the risk of diabetes, obesity and several types of cancer[14]. An inactive lifestyle leads to increased blood cholesterol levels and the accumulation of visceral fat; this is accompanied by an innate and adaptive immunological response at cellular and tissue levels leading to a persistent low-grade vascular inflammation, which is a key regulatory mechanism in the pathogenesis of atherosclerosis[15]. The development of atherosclerosis leads to CAD, which becomes evident when it causes thrombosis, angina pectoris and/or myocardial infarction. Inactivity is also associated with low cardiorespiratory fitness, worse mental health and poor quality of life[16].

Time spent in sedentary activities is also associated with an increased risk of cardiovascular diseases and all-cause mortality[17]. Time spent in sedentary activities and mortality show a dose-response relationship, which means that the risk of mortality increases across greater amounts of time spent in sedentary activities, such as sitting or watching TV[18]. In adults who reported daily sitting time in almost none of the time, one fourth of the time, half of the time, three fourths of the time and almost all the time, the adjusted hazard ratios for cardiovascular mortality were 1.00, 1.01, 1.22, 1.47 and 1.54 ($P < 0.0001$)[18]. It should be noted that the association between sedentary behaviours and mortality is independent of participation in moderate to vigorous leisure-time physical activity[18]. In a recent study, Matthews *et al*[19] showed that excessive amounts of TV viewing (more than 7 h/d *vs* less than 1 h/d) are associated with an increased risk of all-cause and cardiovascular disease mortality, even among adults who reported high levels of moderate to vigorous physical activity (more than 7 h per week). The results of INTERHEART study published recently also demonstrated that subjects who owned both a car and a TV were at higher risk of myocardial infarction (multivariable-adjusted OR = 1.27, 95%CI: 1.05-1.54) compared with those who owned neither[20]. Together,

these data suggest that participation in moderate to vigorous physical activity may not be enough to fully attenuate the independent effect of sedentary activities on increased risk for cardiovascular diseases.

PHYSICAL ACTIVITY IN PRIMARY PREVENTION OF CARDIOVASCULAR DISEASES

It has long been demonstrated that physical activity decreases the likelihood of someone developing CAD and to suffer from its consequences[21]. Seminal studies demonstrated that active conductors were protected against CAD compared with inactive bus drivers[22]. These observations were replicated in active postmen compared with inactive telephonists, indicating that people with active occupations were less likely to have adverse events due to CAD[23]. Several studies extended these findings, and showed that physical activity has a graded inverse association with the risk of coronary events[24,25]. Walking is associated with decreased risk of coronary events, with women walking three or more hours per week at a brisk pace having about 35% lower risk of coronary events than those who walk infrequently[25].

Studies conducted in old aged individuals confirmed that physical activity also reduces significantly mortality risk in elderly people without pre-existent cardiovascular disease[26]. Inactive people who become active later in life have also lower risk of cardiovascular events compared with those who remain sedentary[25]. The relation of changes in physical activity and mortality were also seen in men with pre-existent cardiovascular disease[27]. The magnitude of risk reduction is similar as quit smoking[28]. This shows the importance of adopting active lifestyle behaviours, even if initiated during middle or late adulthood during leisure time, as increased leisure time physical activity reduces the risk of cardiovascular events, such as myocardial infarction[20].

In healthy individuals, some of the benefits that physical activity exerts on the prevention of cardiovascular diseases are attributed to positive modifications on traditional risk factors[29]. Maintaining or improving physical activity prevents weight gains and the development of hypertension, hypercholesterolemia, metabolic syndrome, and diabetes, all of which are important cardiovascular risk factors[30,31]. Indeed, physical activity prevents the development of hypertension in normotensive individuals, but it also reduces blood pressure in hypertensive patients[32,33]. In addition, physical activity is associated with better blood cholesterol levels as well as decreased prevalence of obesity and type-Ⅱ diabetes, all of which contribute to the development of vascular inflammation and atherosclerosis[34]. Many studies have also demonstrated that physical activity reduces blood concentrations of several inflammatory biomarkers such as C-reactive protein, lipoprotein-associated phospholipase A2, cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor-α, many of which have been recognized as important players in the initiation and development of atherosclerosis[35,36].

On the other hand, it was also shown that physical activity might prevent cardiovascular diseases independently of its potential benefit on other cardiovascular risk factors, including obesity, hypertension and diabetes. This could be related with the increase in physical fitness, which also prevents the burden of the cardiovascular diseases independently of the level of physical activity someone performs[37,38]. Improved physical fitness also attenuates the risk of developing hypertension, increased cholesterol and metabolic syndrome[30], suggesting that both physical activity and physical fitness are independent protective elements of cardiovascular events. A summary of the benefits of physical activity in primary prevention is presented in Table 1.

PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK: INVERSE DOSE-RESPONSE RELATIONSHIP

Whether physical activity is associated with the reduced risk of cardiovascular events is beyond question. The issue that countless researchers have been trying to solve is how much physical activity is needed for reducing the risk of cardiovascular diseases.

Landmark studies showed that death rates declined steadily as energy expended on physical activities increased from less than 500 to 3500 kcal/wk[39]. Death rates were one quarter to one third lower in men expending 2000 or more kcal during exercise per week compared with less active men[39]. The inverse dose-response relationship between physical activity and all-cause mortality was confirmed in recent studies and seems to be stronger in women than in men[40,41]. Individuals who exercise for 90 min/wk have a three year longer life expectancy than inactive people[41]. Every additional 15 min of exercise per day promotes a further 4% risk reduction in all cause-mortality[41]. Moreover, recent meta-analysis of previous studies showed that individuals who engage in the equivalent of 150 min per week of moderate intensity leisure time physical activity have 15% to 20% lower risk of developing CAD than those who undertake no leisure time physical activity[42,43]. Those who perform the equivalent of 300 min/wk of moderate physical activity have even greater risk reduction of coronary artery disease. It is important to note that even persons who did 75 min of moderate intensity physical activity per week had reduced risk of cardiovascular disease, lending credence to the notion that some physical activity is better than none and that additional benefits occur with more physical activity[42].

On the other hand, vigorous physical activity leads to lower incidence of CAD and greater reductions in

Table 1 Summary of the benefits of physical activity in primary prevention

Physical activity in primary prevention	
Prevents	**Improves**
Diseases development associated with cardiovascular disease (hypertension, diabetes and metabolic syndrome)	Physical activity levels and physical fitness (cardiorespiratory fitness and skeletal muscle strength)
Obesity	Prevents weight gains, and improves blood cholesterol profile towards increased HDL blood levels and lower LDL blood levels
Type 2 diabetes	Glycemic control, and improves insulin sensitivity in type 2 diabetics
Hypertension	Prevents the development of hypertension in normotensive individuals, and reduces blood pressure in hypertensive patients
Vascular inflammation and atherosclerosis	Reduces blood concentrations of several inflammatory biomarkers such as C-reactive protein, lipoprotein-associated phospholipase A2, cytokines IL-1β, IL-6 and TNF-α

TNF: Tumor necrosis factor; HDL: High density cholesterol; LDL: Low density cholesterol; IL: Interleukin.

all-cause mortality[44,45]. However, not all studies have controlled for exercise volume, advising caution in the interpretation of these results. These results are consistent with the recent recommendations suggesting that healthy adults should perform at least 150 min of moderate intensity aerobic exercise (40%-60% of heart rate reserve) or 75 min of vigorous intensity physical activity (60%-85% of heart rate reserve) per week or through the equivalent combination of moderate and vigorous-intensity physical activities[46]. Very recently, pooled data from population-based prospective cohorts in the United States and Europe, including a total of 661137 men and women, with a median follow-up of 14.2 years, showed that risk of mortality was 20% lower among individuals performing less than the recommended minimum of leisure time physical activity [HR = 0.80 (95%CI: 0.78-0.82)], with this inverse association growing stronger among those reporting 1 to 2 times [HR = 0.69 (95%CI: 0.67-0.70)] or 2 to 3 times the recommended minimum [HR = 0.63 (95%CI: 0.62-0.65)] leisure time physical activity[47]. Interestingly the association appears to reach a threshold among persons performing higher levels of physical activity, suggesting that inactive individuals may benefit from modest amounts of physical activity in terms of reducing mortality while high levels of physical activity does not confer increased risk of mortality[47]. Additionally, maximum longevity benefit seems to be associated with meeting the recommended guidelines for moderate to vigorous physical activity[47]. Health benefits are also achieved when sedentary behaviours are replaced by light intensity physical activity (< 40% of heart rate reserve) and moderate to vigorous activities are held constant[48]. Reducing sedentary activities should be pursued by everyone independent of the amount and intensity of physical activity one achieves per week, as sitting time or time spent watching television is independently associated with greater incidence of cardiovascular risk factors, cardiovascular disease and cardiac mortality[18,49].

PHYSICAL ACTIVITY IN SECONDARY PREVENTION OF CARDIOVASCULAR DISEASES

Physical activity also plays an important role in secondary prevention of cardiovascular diseases by reducing the impact of the disease, slowing its progress and preventing recurrence. Nonetheless, it is difficult to ascertain the role of leisure time physical activity alone in secondary prevention, as most studies have not discerned the effects of structured exercise training alone or incorporated in comprehensive cardiac rehabilitation programs from those induced by leisure time physical activity alone. In patients following myocardial infarction, participation in an 8-wk exercise-based cardiac rehabilitation programme was found to improve leisure-time physical activity levels consistent with health-related benefits[50]. Interestingly, at baseline, only half of the subjects were compliant with physical activity recommendations (52%), but at the end of the intervention, 76% of the exercise group and 44% of controls complied with physical activity recommendations[50]. Likewise, a home-based cardiac rehabilitation program, composed by education and counselling intervention for 12 wk, regarding physical activity and cardiovascular risk factor management, showed an increase in physical activity index and time spent in moderate to vigorous physical activity during the intervention period with no changes in the control group[51].

Despite the well-known benefits of physical activity and exercise training, most of eligible cardiovascular patients do not benefit from cardiac rehabilitation programs[52], and these patients are more likely to taking less exercise[53]. Exercise levels may even decrease after the diagnosis of heart disease. The least active subjects are more likely to be older, male, obese and present symptoms during common activities such as short distance walking[53].

Participation in cardiac rehabilitation programs has been associated with decreased mortality and recurrent myocardial infarction, with compliant patients showing greater risk reduction when compared to patients with less attendance to exercise training sessions[54,55]. A recent meta-analysis including patients who have had myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris or CAD defined by angiography confirmed that exercise-based cardiac rehabilitation programs are effective in reducing total and cardiovascular mortality (in medium and long term) and hospital admissions (in

shorter term) but not the risk of myocardial infarction and revascularization[56]. Even though smoking cessation and nutritional counselling can also contribute for these positive outcomes, exercise training has an independent effect in the prevention of cardiovascular death[57]. Exercise-based cardiac rehabilitation programs promote an increase in cardiorespiratory fitness, a strong predictor of all-cause mortality, but also increase leisure time physical activity levels[51]. Hambrecht *et al*[58] demonstrated that estimated energy expenditure during leisure time physical activity is correlated with changes in coronary stenosis diameter independent of attendance in formal exercise interventions. Energy expenditure was lower in patients with progression of coronary atherosclerosis, higher in patients with no change, and highest in patients with regression of coronary stenosis diameter. High workloads were needed (about 1500 kcal/wk) to halt progression of coronary atherosclerosis, and regression of atherosclerosis was observed only in patients expending an average of 2200 kcal/wk in leisure time physical activity, corresponding to approximately 4 to 6 h of moderate intensity physical activity per week. A summary of the benefits of physical activity in secondary prevention is presented in Table 2.

Table 2 Summary of the cardiovascular protection mechanisms induced by physical activity in secondary prevention

Physical activity in secondary prevention	
Decreases	**Increases**
Resting heart rate	Heart rate reserve
Resting systolic blood pressure	Diastolic function
Myocardial oxygen demand	Coronary circulation
Risk of myocardial ischemia	Myocardial perfusion
Sympathetic tone	Parasympathetic activity
Arterial Stiffness	Endothelial function
Low-grade vascular inflammation (levels of pro-inflammatory cytokines)	Nitric oxide bioavailability and circulating levels of endothelial progenitor cells
Expression of reactive oxygen species	Expression and activity of anti-oxidant enzymes
Resting levels of plasminogen activator inhibitor type 1	Resting levels of tissue plasminogen activator activity
Platelet adhesion and aggregation	

CARDIOVASCULAR PROTECTION MECHANISMS INDUCED BY PHYSICAL ACTIVITY IN SECONDARY PREVENTION

It is well established that physical activity lowers resting heart rate and systolic blood pressure and increases heart rate reserve in patients with heart disease[59,60], thereby decreasing myocardial oxygen demands and preventing myocardial ischemia for a given absolute exercise intensity[61]. This may stem from a restored function of the autonomic nervous system towards lower sympathetic tone and enhanced parasympathetic activity[60,62]. In addition, aerobic physical activity improves myocardial perfusion in CAD patients, as a result of improved endothelial function, enhanced coronary circulation and vasomotor responses to vasoactive substances[63].

Aerobic physical activity seems to improve endothelial function in response to increases in blood flow-mediated shear stress, stimulating the endothelial production of nitric oxide and preventing its degradation by reactive oxygen species[64]. In addition, physical activity mitigates vascular inflammation while it improves anti-oxidant defences, also contributing for improving endothelial dysfunction[64-66]. Physical activity also promotes the mobilization of endothelial progenitor cells into the circulation to maintain endothelial integrity and stimulate vascular regeneration and endothelial repair[67,68].

Arterial stiffness has also been shown to decline in active individuals[69], as well as in CAD patients after cardiac rehabilitation[70,71], changes that may reduce aortic systolic blood pressure and cardiac afterload, increasing coronary perfusion and preventing myocardial ischemia as a result. A recent randomized controlled trial did not find significant changes between groups in arterial stiffness after an 8-wk exercise training program in post-myocardial infarction patients under optimized medication; however, when excluding those patients who did not attend, at least 80% of the exercise sessions, the authors found a significant reduction in arterial stiffness when compared to the control group[72].

In addition, a sedentary lifestyle during healthy aging is associated with decreased left ventricular compliance, leading to diminished diastolic performance, while prolonged, sustained endurance training seems to preserve ventricular compliance with aging[73] and to enhance diastolic function in heart failure patients[74,75]. Moderate to vigorous physical activity may also offer protection against cardiac events by inducing short-term transient ischemia, conferring a window of protection against an ischemic insult of longer duration, a phenomenon known as cardiac preconditioning[76,77]. It has been demonstrated in patients with old myocardial pectoris or angina pectoris that a single bout of physical exercise is capable of reducing exercise-induced ST-segment depression[78]. Prevention of coronary events may also stem from antithrombotic effects, even though evidence supporting an association between regular physical activity and decreased risk of thrombus formation and plaque rupture is scarce[79].

Acute strenuous physical activity seems to be associated to increased platelet adhesiveness and aggregation, increased thrombin formation and increased activity of several coagulation factors[80,81]. Nonetheless, regular moderate physical activity has been shown to blunt platelet adhesion and aggregation in healthy sedentary individuals[82] and heart failure patients[83]. Blood coagulation prospect after plaque rupture appears to diminish with regular physical activity, with studies finding lower plasma levels of several haemostatic factors in active individuals and women with CAD[84,85]. Inverse dose-response association between physical

activity and circulating levels of fibrinogen has been reported[86] and regular aerobic exercise seems to increase resting tissue plasminogen activator activity and to reduce plasminogen activator inhibitor type 1 in older adults[87,88].

SUMMARY

Physical inactivity is one of the four leading risk factors of non-communicable diseases, in particular those related with cardiovascular diseases such as acute coronary syndromes, stroke and heart failure. Despite this evident association, prevalence of physical inactivity is still elevated worldwide, being directly responsible for almost one tenth of premature death from non-communicable diseases. Even though physical activity has been shown to play an important role in primary and secondary prevention of cardiovascular diseases and major cardiovascular events, regular participation in physical activity is still below the necessary threshold to improve cardiorespiratory fitness and confer cardiac protection in many subjects. Reducing sedentary behaviours and performing less than the recommended minimum leisure time physical activity may be sufficient to reduce mortality, but meeting the recommended guidelines of moderate- or vigorous-intensity physical activities and reducing sedentary behaviours is associated with higher health benefits. Therefore, health professionals and policy makers in public health should align strategies to increase participation in physical activity, especially among those who show less interest or availability to engage in regular physical activity.

FUTURE PERSPECTIVES

The above-mentioned results are promising and provide good perspectives for the future.

Over the last decades the standard of living and physical activity profile performed throughout the day has been changing in societies around the world in parallel to the high death rates caused by CAD. Recent studies have addressed the time spent in sedentary behaviours as a risk factor for CAD, regardless of the amount and intensity of physical activity done. Taking these data into consideration, future studies should addresses both the causes and effects of both sedentary behaviour and physical inactivity in bodily adaptations and its relations with the development of cardiovascular disease.

It is also suggested that future studies evaluate the relationship between different covariates that may influence the effects of physical activity, such as age, sex, ethnicity, educational and/or socioeconomic status, and occupational and leisure-time contexts, in order to identify more assertively public health intervention strategies so that physical activity and exercise programs can be optimized for reducing the number of deaths caused by cardiovascular complications.

Although substantial evidence exists demonstrating the benefits of exercise training, referral to and participation in cardiac rehabilitation programs is still less than half among all eligible patients with cardiovascular diseases. Thus, more research is needed to identify common barriers to participation in physical activity programs, not only in the general population but also in special populations and minorities, and to understand how such barriers can be broken down to increase participation in physical activity.

Thus, we believe that such strategies could have important beneficial effects on the reduction of deaths caused by cardiovascular disease from the primary and secondary prevention.

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