PHYSICAL ACTIVITY FOR THE PREVENTION OF CARDIOVASCULAR DISEASES

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FIZIČKA AKTIVNOST U PREVENCIJI KARDIOVASKULARNIH OBOLJENJA

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Received / Primljen: 22. 03. 2016. Accepted / Prihvaćen: 03. 07. 2016.

ABSTRACT

Over the last decade, the quantity and quality of scientific literature examining the relationship between physical activity (PA) and cardiovascular diseases (CVD) have significantly increased. Data from the literature now unequivocally show that physical inactivity is one of the major risk factors for CVD. It is believed that obesity, the prevalence of which has tripled over the last three decades, and physical inactivity among children are the main factors that will increase the prevalence of CVD in this century. The cardiovascular benefits of exercise are multifactorial and include important systemic effects on skeletal muscle, the peripheral vasculature, metabolism, and neurohumoral systems, as well as beneficial alterations within the myocardium itself. Thus, exercise does much more than change traditional risk factors, such as blood pressure, blood lipids, glucose tolerance and insulin resistance, metabolic syndrome, and overweight and obesity. Evidence from epidemiologic studies suggests that the preventive effects of PA may be achieved by 150 minutes of moderate PA a week, while increases in the intensity and volume of exercise lead to further health benefits. This dose–response gradient is curvilinear, with the largest gains from the first hour of weekly exercise. However, although much progress has been made in this field, existing studies performed on human subjects do not clearly show what type, intensity, and duration of exercise is most beneficial to cardiovascular fitness and metabolic optimization. Animal-based exercise studies may provide more information and help to elucidate the abilities of different training regimens to reduce the risk of CVD.

Keywords: *cardiovascular diseases, physical activity, physical fitness, prevention*

SAŽETAK

Kvantitet i kvalitet naučne literature na temu veze između fizičke aktivnosti i kardiovaskularnih oboljenja (KVO) značajno je porastao u toku poslednje decenije. Naučni podaci sada nedvosmisleno pokazuju da je nedovoljna fizička aktivnost jedan od glavnih faktora KVO rizika. Smatra se da su gojaznost, čija se prevalenca u poslednje tri decenije utrostručila, i fizička neaktivnost dece glavni faktori rizika koji će u 21. veku povećati prevalencu ovih oboljenja. Kardiovaskularni benefiti vežbanja su multifaktorijalni, i uključuju važne sistemske efekte na skeletne mišiće, perifernu vaskulaturu, metabolizam, neurohumoralni sistem, kao i promene u samom srčanom mišiću. Dakle, efekti vežbanja se ne ogledaju samo u promeni tradicionalnih KVO risk faktora kao što su krvni pritisak, lipidni profil, tolerancija glukoze, rezistencija na insulin, metabolički sindrom, prekomerna uhranjenost i gojaznost. Dokazi dobijeni iz jakih epidemioloških studija ukazuju na to da se preventivni efekti fizičke aktivnosti mogu postići umerenom fizičkom aktivnošću od oko 150 minuta nedeljno, dok se sa povećanjem obima ili intenziteta fizičke aktivnosti dobijaju dodatni zdravstveni benefiti. Ovaj dozno-zavisni gradijent je krivolinijski, a najveći zdravstveni benefiti dobijaju se implementacijom prvog sata vežbanja nedeljno. Ipak, iako je napravljen veliki napredak na ovom polju, postojeće studije sprovedene na humanoj populaciji ne pokazuju jasno koji tip, intenzitet i obim vežbanja je najefikasniji u povećanju kardiovaskulanog fitnesa i metaboličkoj optimizaciji. Animalni modeli vežbanja bi mogli pružiti više informacija i pomoći u rasvetljavanju benefita različitih trenažnih režima u smanjenju rizika od KVO.

Ključne reči: *kardiovaskularna oboljenja, fizička aktivnost, fizički fitnes, prevencija*

DE GRUYTER OPEN

UDK: 616.12-084; 613.71/.74 / Ser J Exp Clin Res 2017; 18 (2): 99-109
DOI: 10.1515/SJECR-2016-0049

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ABBREVIATIONS

ACSM - American College of Sports Medicine
AHA - American Heart Association
BP - blood pressure
CRP - C-reactive protein
CVD - cardiovascular diseases
CHD - coronary heart disease
eNOS - endothelial nitric oxide synthase
ET-1 - endothelin-1
HbA1c - glycated haemoglobin
HDL-C - high-density lipoprotein cholesterol
IL-6 - interleukin-6
LDL-C - low-density lipoprotein cholesterol
NO - nitric oxide
PA - physical activity
PF - physical fitness
ROS - reactive oxygen species
TNF - tumour necrosis factor
T2D - type 2 diabetes
WHO - World Health Organization

PHYSICAL ACTIVITY/FITNESS AND HEALTH

Physical activity (PA) and physical fitness (PF) have been linked with health and longevity since ancient times. A positive correlation between PA and health was recognized more than 4000 years ago in China, but Greek physicians of the 5th and 4th centuries BC were the ones who established a tradition of maintaining positive health through the combination of diet and exercise. Currently, physical inactivity, poor diet and smoking are the root causes of approximately one-third of deaths in developed countries (1). These risk factors often underlie today's leading chronic disease killers of heart disease, stroke, diabetes and cancer.

The strength of the association between PF and all-cause mortality risk, which has been reported in numerous epidemiological studies, suggests that PF is of equal or greater importance as a mortality predictor than other established disease risk factors. Nevertheless, the Norwegian epidemiologist Gunnar Erikssen asserts that "modern day humans are dying because of a lack of physical exercise" (2). The World Health Organization (WHO) reported that physical inactivity is the 4th leading risk factor for global mortality, accounting for 6% of deaths globally (3). Recently, a published analysis of the worldwide burden of disease showed that physical inactivity is responsible for 6% of the incidence of coronary heart disease (CHD), 7% of type 2 diabetes (T2D), 10% of breast cancer, and 10% of colon cancer (4). It is posited that physical inactivity among children and obesity, the prevalence of which has tripled in the last 30 years, are the main risk factors that will increase the prevalence of these diseases in the 21st century (1). However, although PA and PF are associated with the prevention of premature mortality, they do not appear to extend the natural lifespan (1).

PHYSICAL ACTIVITY/FITNESS AND CARDIOVASCULAR DISEASES

Advances in understanding the pathophysiological basis of cardiovascular diseases (CVD) have led to significant reductions in the prevalence and incidence of these diseases since the middle of the last century (5), but CVD still represent the main cause of death worldwide (6), especially in Eastern Europe (7). In Europe, approximately 42% of deaths in women and 38% in men are due to CVD (8), mostly CHD and stroke. Although genetic factors and age play major roles in the occurrence and development of these diseases, other factors, such as elevated blood pressure (BP), high levels of cholesterol, insulin resistance, diabetes, obesity and behavioural factors such as smoking, poor diet and physical inactivity, also have a great influence on CVD development (9).

The observation that PA can protect against heart attack was first made in the 1950s, when the first cross-sectional studies compared incidence rates of CHD attacks in men in a variety of occupations. One of the first studies reported that the conductors of English double-decker buses experienced roughly half the number of heart attacks as the drivers (10). A similar difference was noticed between postmen and their sedentary colleagues who sorted the mail (11). Since the early work of Morris and colleagues (10,11), from the works of Blair, Paffenberger and colleagues in the 1980s and 1990s (12-15) to today, numerous longitudinal studies have explored the correlation between PA/PF and the relative risks of morbidity and mortality (16-20). The US Physical Activity Guidelines Advisory Committee reported that, based on analysis of 60 studies with a total of more than 300 000 participants, moderate PA decreases the risk of CHD by 19% in males and 22% in females, while vigorous exercise has even better effects, with a 32% reduction among males and a 38% reduction among females (21). Similar results were reported on the relationship between PA and stroke (22-24). There was no evidence on different effects of PA in different populations, including men vs women, premenopausal vs postmenopausal women, or middle-aged vs older (>65 years) populations. Those results are consistent with the systematic review and meta-analysis on the association of PA with all-cause and cardiovascular mortality, which included 24 studies with a total of more than 650 000 participants (25). This analysis showed that cardiovascular mortality was 35% lower in the most active compared with the least active subjects. Adjusting only for age, the risk reduction increased to 47%. In stud-

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ies that examined CVD risk based on PF (results achieved on a test of cardiovascular endurance) as opposed to data on the amount and intensity of PA reported by questionnaire, PF was related to a 57% lower CVD risk (26). The key message obtained from those studies is that, in sedentary subjects, even small increases in PA, and consequently PF, significantly reduce CVD risk (27). One of the first studies to demonstrate an association between PF and all-cause mortality risk was the Aerobics Center Longitudinal Study (12). In this study, based on time to exhaustion in a maximal treadmill exercise test, subjects were classified into 5 groups of fitness. The results showed that the risk of all-cause mortality during follow-up was 3.44 times higher in men and 4.65 times higher in woman with lowest physical fitness level when compared to subjects with the highest fitness level, but more importantly, even small improvements in fitness among totally unfit subjects reduced the risk by half. These trends remained after statistical adjustment for age, smoking, cholesterol level, systolic BP, fasting blood glucose level, parental history of CHD and follow-up interval. A 2012 analysis of data from 6 cohorts with a total of 655 000 adults followed for a median of 10 years supports the idea that even minimal levels of physical activity can extend lifespans (28). Compared with their inactive peers, women who reported a low amount of PA (~11 minutes/day) had a 2.1-year longer life expectancy after age 40, while women who exercised 30 minutes/day had additional gains in life expectancy (3.6 years). Women with an activity level of 60 to 90 minutes/day experienced further gains (4.0 years), proving that the dose–response gradient is curvilinear, with the largest gains from the first hour of weekly exercise. The weight of the evidence from numerous studies strongly points towards a favourable relation between increases in habitual aerobic exercise and cardiovascular health outcomes, including CHD morbidity and mortality, stroke, control of BP, atherogenic dyslipidaemia, vascular function measures and cardiorespiratory fitness (21).

PHYSICAL ACTIVITY AND REDUCED CARDIOVASCULAR RISK: BIOLOGICAL MECHANISMS

The cardiovascular benefits of exercise are multifactorial and include important systemic effects on skeletal muscle, the peripheral vasculature, metabolism, and neurohumoral systems, as well as beneficial alterations within the myocardium itself (29, Table 1). Molecular mechanisms through which exercise exerts its favourable effects on CVD are clearly presented in a recent paper by Gielen and colleagues (30). Thus, exercise does much more than change traditional risk factors such as BP, blood lipids, glucose tolerance and T2D, metabolic syndrome, and overweight and obesity (31). For example, in the women's health study (32), less than half of the improvement in the risk for CHD could be attributed to improvements in traditional risk factors. Additionally, only ~59% of the risk reduction for all forms of CVD could be attributed to the effects of exercise on traditional factors. This means

Table 1. Effects of physical activity on the cardiovascular system (30)

PHYSICAL ACTIVITY			
Cardiac effects	**Vascular effects**	**Neurohumoral and autonomic effects**	**Non-cardiovascular effects**
Normal LV function: Ischaemia/reperfusion protection Prevention of age-related diastolic dysfunction Physiologic hypertrophy *Systolic heart failure:* Reverse left ventricular remodelling Left ventricular ejection fraction ↑ Improved neurohumoral activation Arrhythmia prevention *Diastolic heart failure:* Prevention of diastolic function Improvement of left ventricular relaxation and compliance *Cardiac valves:* Prevention of valve degeneration Prevention of calcification	*Aorta:* Aorta stiffness ↓ Aortic compliance ↑ *Conduit vessel:* Endothelial vasodilatation ↑ Production of nitric oxide ↑ Oxidative stress ↓ *Resistance vessel and microcirculation:* Vasculogenesis Sensitivity to adenosine ↑ *Capillary bed:* Capillary vessel formation ↑ *Venous circulation:* Venular capillaries ↑ *Pulmonary artery:* Endothelial function ↑ Pulmonary artery pressure in CHF ↓	Sympathetic tone ↓ Parasympathetic tone ↑ *In chronic heart failure:* Norepinephrine Angiotensin II Atrial natriuretic peptide Brain natriuretic peptide *Antiarrhythmic effects:* Normalization of heart rate variability Hyperpolarization Attenuated automaticity	*Skeletal muscle:* Oxidative phosphorylation ↑ Muscle hypertrophy Calcium handling ↑ *Ventilation:* Vital capacity ↑ Tidal volume ↑ Max inspiratory and expiratory force ↑ *Haemorheology:* Blood viscosity ↓ Coagulability ↓ O_2 transport capacity ↑

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that only ~40–60% of the relative risk of CHD and CVD in general can be explained by how exercise and PA modify traditional risk factors.

PA and BP. Despite being healthy, physically inactive people and people with poor fitness levels have a 30% higher risk of developing high BP compared with healthy physically active/fit people (33). Furthermore, for every 20/10-mmHg increase in BP, there is a doubling of mortality from both ischaemic heart disease and stroke (34). A recently published meta-analysis (35) shows that in healthy people, aerobic types of PA decrease resting BP by an average of 2.4/1.6 mmHg (systolic/diastolic BP). In prehypertensive subjects, the corresponding decrease is 3.1/1.7 mmHg, and in hypertensive subjects it is 6.9/4.9 mmHg. Resistance training can also induce lowering of BP (36). It has been long thought that static resistance exercises should be avoided due to an acute hypertensive response, but recent research shows that this type of exercise has the greatest potential for systolic BP reduction (37). A meta-analysis of randomized controlled trials shows that resistance training reduces systolic BP by an average of 3.2 mmHg and diastolic BP by an average of 3.5 mmHg (38). Although these reductions seem modest, a systolic BP reduction of 3 mmHg in average populations has been estimated to reduce cardiac morbidity by 5-9%, stroke by 8-14%, and all-cause mortality by 4% (36). BP lowering is the result of the reduction in total peripheral resistance due to changes in the diameter of blood vessels, which are attributed to the smaller influence of the sympathetic system on the peripheral blood vessels and the effects of local vasodilators such as nitric oxide (39).

PA and blood lipids. The role of blood lipids in the pathology of atherosclerosis is well established, and dyslipidaemia is understood to be an important contributing factor for CHD. Cross-sectional studies have consistently shown a positive association between the volume and intensity of aerobic activities and high-density lipoprotein cholesterol (HDL-C) levels and a negative association with triglyceride levels (40), especially in subjects with initially high levels of these blood lipids (26). A meta-analysis of 52 exercise training trials demonstrated an average increase in HDL-C levels of 4.6% and average reductions in triglyceride and low-density lipoprotein cholesterol (LDL-C) concentrations of 3.7% and 5.0%, respectively (15,16). In contrast, the effects of resistance training on blood lipids are not as consistent in the available literature (41).

PA and T2D. A great number of studies have shown that PA is significantly related to improved glucose tolerance and decreased risk of T2D (21, 26), which is a consequence of increased sensitivity of muscle and other tissues to insulin. A meta-analysis of 10 cohort studies with a total of more than 300 000 participants found that compared with inactivity, and after adjustment for body mass index, moderate-intensity PA predicted a 17% reduction in diabetes risk (42). In one study, brisk walking for 30 minutes/day 5 days/week was associated with a 25% reduction in diabetes risk (43), while another stated that participants who walked 2 to 3 hours/week were 34% less likely to develop diabetes (44). Cardiorespiratory fitness, as assessed by a bicycle ergometer or treadmill test, also correlates inversely with the incidence of T2D (45). The effects of resistance exercise on T2D risk remain unknown due to few published studies on this relationship. One study found that resistance training was associated with a decline in glycated haemoglobin (HbA1c) levels, which are measured primarily to identify the average plasma glucose concentration over prolonged periods of time (46). Although the effects of resistance training on T2D risk are not clearly proven scientifically, leading organizations for diabetes prevention and treatment recommend that diabetics include this type of exercise in their lives (47).

Exercise also has a role in secondary prevention in subjects with T2D. Heart disease and stroke account for approximately 65% of deaths among people with diabetes, and individuals classified as prediabetic are also at increased risk for CVD (34). Recent meta-analyses of diabetic cohorts report risk reductions of 29% for CVD incidence (48) and 37% for CVD mortality (49) for those in the highest versus lowest PA category. Walking 2 to 4.5 hours/week is associated with a 46% reduction in CVD mortality compared with walking less than 2 hours/week (49). Structured exercise training that consists of aerobic exercise, resistance training, or both, is associated with HbA1c reduction in patients with type 2 diabetes (36). A review of 9 trials examining the effect of exercise training in patients with T2D reported an average reduction of HbA1c of 0.5% to 1% (50). One study showed that each percentage point reduction in HbA1c was associated with a 35% reduction in microvascular complications (51), whereas an increase of 1 percentage point in HbA1c was associated with a 28% increase in mortality risk, independent of other CV risk factors (52).

Finally, taking into consideration the effects of PA on BP, blood lipids and glucose tolerance, it is clear that there is a strong relationship between the amount of PA and metabolic syndrome. Several cross-sectional and prospective studies strongly suggest dose-response relationships between the amount of PA and metabolic syndrome in men and women (21).

PA and obesity. Exercise serves to counteract excess caloric consumption, thereby reducing the risks of obesity. Numerous longitudinal epidemiological studies have found that PA levels are negatively correlated with weight gain (53-55). Prevention of weight gain is an effective way to prevent the development of undesirable changes in the metabolic CVD risk factors, and even small (less than 3%) or no decrease in body weight as a result of PA leads to significant beneficial changes in those risk factors (56). Furthermore, PA also counterbalances the risk caused by overweight (BMI of 25.0 to 29.9) on CVD mortality or events (57). Increasing PA levels from low to moderate ensures a maintenance of body weight, while increasing PA levels from low to high helps individuals lose weight (58). In the Women's Health Study, 60 minutes/day of moderate PA was associated with maintenance of weight or an increase in minor weight loss (less than 2.3 kg) during 13 years of follow up (59). Anoth-

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er study showed that PA for 30 or more minutes per day is strongly associated with a significantly lower likelihood of weight gain of more than 5%, with the strongest effect in overweight subjects (60). In this study, even a small increase in activity (11-20 minutes/day) in sedentary subjects appeared to be beneficial. Resistance exercise also positively influences the maintenance of weight, although evidence from the literature is less consistent than in the case of aerobic activity. Muscle mass decreases with age, but resistance training increases muscle mass and consequently increases resting energy consumption (61). Weight loss induced by resistance training is not as obvious due to the simultaneous decrease in fat mass and increase of muscle mass (36), meaning that although weight does not significantly change, body composition improves.

Aerobic PA also decreases total abdominal adiposity and intra-abdominal adiposity (26). This is important because excessive central adiposity, especially visceral fat, is related to the development of hyperlipidaemia, hypertension, insulin resistance, T2D, and cardiac diseases, while fat in the extremities is a small risk factor (62, 63). Although there is genetic predisposition to having visceral fat tissue, ageing, together with a high-fat diet and sedentary lifestyle, are also important determinants of this fat tissue. According to limited scientific evidence, the effects of resistance training on abdominal obesity seem to be small and inconsistent (21, 36).

PA and inflammation. An inactive lifestyle leads to the accumulation of visceral fat, and this is accompanied by adipose tissue infiltration by pro-inflammatory immune cells, increased release of adipokines and the development of a low-grade systemic inflammatory state (64). A chronic low-grade inflammatory state, as indicated by elevated levels of circulating inflammatory markers such as interleukin-6 (IL-6), tumour necrosis factor (TNF) and C-reactive protein (CRP), has been established as a predictor of risk for numerous diseases, including CVD. Regular exercise reduces the risk of chronic metabolic and cardiorespiratory diseases, partially due to the anti-inflammatory effects of PA. PA has been shown to decrease chronic low-grade inflammation, which is an important factor in the pathogenesis of atherosclerosis and insulin resistance (65, 66). The anti-inflammatory effects of regular exercise may be mediated via both a reduction in visceral fat mass (with a subsequent decreased release of adipokines) and the induction of an anti-inflammatory environment (67-69). Following acute exercise, there is a transient increase in circulating levels of anti-inflammatory cytokines, whereas chronic exercise reduces basal levels of pro-inflammatory cytokines (65). Cross-sectional studies indicate that increasing levels of PA/PF are associated with reductions in circulating levels of TNF-α and IL-6 and increased levels of anti-inflammatory substances such as IL-4 and IL-10 (70-72). Cross-sectional studies also consistently demonstrate an inverse relationship between serum CRP and both PA level and cardiorespiratory fitness (73). For example, one study found that 10 months of aerobic exercise, but not flexibility and resistance exercise, significantly reduced serum CRP by 10–15% (74). Exercise training also induces the expression of antioxidant and anti-inflammatory mediators in the vascular wall that may directly inhibit the development of atherosclerosis (65).

PA and oxidative stress. Atherosclerosis has been described as an inflammatory response to oxidized LDL in the artery wall (75). Although acute exercise increases production of reactive oxygen species (ROS), exercise-induced plasma oxidative stress may stimulate an arterial antioxidant response, which should inhibit LDL oxidation, inflammation and ultimately atherosclerosis (76). Chronic exercise appears to enhance antioxidant defences in skeletal muscle, the circulation and the vasculature by a variety of mechanisms. Regular exercise training increases the activity of the antioxidant enzymes glutathione peroxidase, superoxide dismutase and catalase (77). Chronic exercise also reduces markers of oxidative stress in the plasma, including F2-isoprostanes (78) and myeloperoxidase (79), whose circulating levels are also associated with CVD risk (80,81). Furthermore, exercise increases the activity of endothelial nitric oxide synthase (eNOS), whose activity has many direct and indirect effects on oxidative stress and inflammation (65). Exercise-induced upregulation of vascular eNOS expression is closely related to the frequency and intensity of physical forces within the vasculature, especially shear stress. Laminar flow, which is augmented during moderate and intense physical activities, upregulates eNOS expression, while oscillatory forces, which are associated with hypertension, lead to increased NADPH-oxidase activity and augment oxidative stress (82).

PA and arterial stiffness and compliance. PA also exerts several direct effects on the vascular wall. Adults who regularly perform aerobic PA demonstrate smaller or no age-associated increases in large elastic artery stiffness, reductions in vascular wall endothelial function, and increases in carotid artery intimal medial thickness (26, 83, 84). Aerobic exercise training improves carotid artery compliance and improves vascular endothelial function through several mechanisms. The effects of exercise on the vascular wall may be induced via the impact of repetitive increases in shear stress on the endothelium, which transduce structural and functional adaptations that decrease arteriosclerotic risk. The age-related losses in endothelial function are also affected by restoration of nitric oxide (NO) availability consequent to prevention of ROS production due to regular PA (85). An exercise-induced increase in arterial compliance is also mediated by a reduction in plasma endothelin-1 (ET-1) concentration, as well as the elimination of ET-1-mediated vascular tone (82). The beneficial effects of PA on the vascular wall may also be enhanced by decreased sympathetic and increased parasympathetic outflow caused by PA (31, 86). When aerobic exercise is combined with resistance training, there is no evidence of increased arterial stiffness (87), though less is known about the independent effects of resistance training on arterial stiffness. The results of the studies on this relationship are contradictory (88, 89).

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RECOMMENDATIONS ON THE TYPE AND DOSE OF PA FOR CVD PREVENTION

Being physically active does not necessarily mean playing sports. PA is defined as any bodily movement produced by skeletal muscles that results in an energy expenditure significantly beyond resting level (such as cleaning or digging), while systemic execution of PA for a specific purpose, i.e., maintenance or development of one or more fitness components, is termed exercise or exercise training (90). PF is a set of attributes that enables an individual to perform PA, and it encompasses cardio respiratory fitness, muscular strength, muscular endurance, flexibility, and body composition as the most important health-related components (91). The effects of exercise training may vary with different exercise modalities (like endurance training or resistance exercise) and dose parameters, specifically programme length, session duration, frequency, and workload or intensity. Dynamic aerobic endurance exercise involves large muscle groups in dynamic repetitive activities that result in substantial increases in heart rate and energy expenditure (37). Resistance training is an activity in which each effort is performed against a specific opposing force generated by resistance and is designed specifically to increase muscular strength, power, and/or endurance (37).

According to the WHO, a significant decrease in CVD risk may be achieved by moderate-intensity aerobic PA (3-6 times higher oxygen consumption than at rest) performed at least 5 days per week for 30 minutes per day (150 minutes per week), and increases in intensity and/or volume of PA provide additional health benefits (92). However, the shapes of any dose-response relations have not been well defined, potentially because of the inaccuracy involved in assessing physical activity (data regarding the amount of PA is usually self-reported by subjects; pedometers, heart rate monitors and other modern technologies are rarely used for monitoring PA in those studies). Additionally, the obtained data are hard to analyse due to the variability of human subjects and numerous confounding factors. Thus, it is not clear what type, intensity, and duration of exercise is most beneficial to cardiovascular fitness and metabolic optimization. The existing data in the literature mainly concern the relationship between CVD prevention and volume of exercise, with less information about intensity and none for frequency and duration of sessions. Many studies suggest that moderate exercise intensity is sufficient to reduce the risk of CVD, but a recent review article suggests that high-intensity aerobic interval training results in a greater beneficial adaptation of the heart compared with that observed after low-to-moderate exercise intensity (93). In a study of health professionals, high exercise intensity was associated with reduced all-cause mortality independent of the duration of activity (17). Another study showed that a single weekly bout of high-intensity exercise reduced the risk of cardiovascular death by approximately half, and no additional benefit from increasing the duration or the number of exercise sessions per week was observed (94). However, it is important to understand that among individuals with very low fitness or with physical limitations, vigorous physical activity may be difficult to achieve and may be contraindicated in some cases. Furthermore, there is very limited data related to the effects of short bouts of PA (~10 min or less) or the accumulation of those shorts bouts during the day, though they seem to be effective in increasing cardio-respiratory fitness (21). One prospective study in men examined the relation between brief bouts of exercise and clinical CVD. After controlling for total energy expenditure, exercise sessions lasting 15, 30, or 45 minutes offered equal protection against incident CVD in subjects followed for 5 years (95). Incorporating such findings into public health messages may help convince busy individuals to treat exercise as a manageable part of their daily routine rather than as a time-consuming activity reserved for rare occasions (96).

Aerobic exercise, such as walking, cycling and stair climbing, was the type of PA that the majority of studies explored in relation to CVD prevention. A meta-analysis that explored active commuting and cardiovascular risk showed that people who walk or cycle to work have an 11% lower risk from CVD mortality, CHD, stroke, hypertension and diabetes (97). Walking, which is the most common and feasible type of PA, has been the most often investigated, and the results of those studies are unambiguous (27, 97-99). The effects of walking on CVD mortality are dose-dependent (98), with the pace of walking being a more important factor than total distance (26). Walking for just 1 hour per week was associated with a reduced risk of CVD outcome (27), while 30 minutes of normal walking each day for 5 days per week (150 minutes per week) was associated with a 19% lower risk of CVD (99). Cycling, as a popular leisure time activity and in some countries a mode of commuting, has been investigated to a lesser extent than walking, and due to some methodological problems, the results of those studies are not as strong. However, evidence from randomized controlled trials indicates that the intensity of the spontaneously chosen speed of cycling is more important than the intensity of walking, and it is sufficient to lead to significant increases in aerobic capacity and to induce favourable changes in selected cardiovascular risk factors. In one prospective study, the risk of fatal and non-fatal CVD incidence among cyclists compared with non-cyclists was found to be 18% (100), while in other studies it was 25-37% (101). Stair climbing, which is a high-intensity aerobic activity, was also found to be effective for improving cardiorespiratory fitness and preventing CVD (102). Stair climbing for 8–12 minutes a day may improve aerobic capacity in previously untrained individuals by more than 10%, which may be associated with a 15% reduction in CVD mortality (103).

In contrast, no large epidemiological studies have explored the relationship between CVD and anaerobic

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exercise, such as strength (resistance) training or short-distance running. However, it is believed that resistance exercise may lower the risk for CHD (104). For example, among 44 000 men in the Health Professionals Follow-up Study, those who trained with weights for more than 30 minutes per week were 23% less likely to develop CHD during an 8-year follow-up period than those who did not train with weights (105). However, although additional research is needed to confirm this protective effect, the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) have published a report in which, in addition to the previously recommended 30 minutes of daily moderate aerobic activity, more intensive aerobic activity and 2 sessions of resistance training per week are added to the recommendations (106). Their inclusion of resistance training for CVD prevention and reduction was based on the known effects of resistance training on certain biological CVD risk factors (36,104). Using scientific evidence and expert opinion, the AHA and the ACSM published guidelines on resistance training for individuals with and without CVD (107, 108). The guidelines for individuals without CVD is to include 2-3 sessions of resistance training per week, each consisting of 8-10 exercises covering the major muscle groups, with moderate training load (30-40% of one repetition maximum for upper body exercises and 50-60% of one repetition maximum for lower body exercises). Exercisers should aim for 8 to 10 repetitions in a set, and when 12 to 15 repetitions can be accomplished with little difficulty, the weight should be increased (36).

PA and BP. For the prevention and management of hypertension, leading health organizations recommend regular aerobic physical activity, such as brisk walking, at least 30 minutes per day, most days of the week (109). Vigorous exercise was not found to be different from moderate-intensity exercise in its ability to reduce blood pressure, with some studies showing that exercise at 40% of oxygen consumption reserve produces a greater reduction in systolic blood pressure than exercise at 65-75% of oxygen consumption reserve (110,111).

PA and blood lipids. There is no general consensus on the optimal exercise prescription for improving the blood lipid profile, as very few studies attempted to evaluate the relationship between training load and blood lipids. However, in the majority of available studies on this theme, the exercise intervention was performed at moderate to high intensity, 3 to 5 times per week, for at least 30 minutes per session.

PA and T2D. To improve glycaemic control, assist with weight maintenance, and reduce risk of CVD, 150 minutes of moderate-intensity, or 90 minutes of vigorous-intensity aerobic PA per week is recommended (34). The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity. Any amount of PA is better than no activity, but higher intensity and more frequent exercise sessions increase this preventive effect. Unless contraindicated, people with T2D should be encouraged to perform resistance exercise 3 times per week, targeting all major muscle groups (34).

PA and obesity. Although there is large inter-individual variability, the literature suggests that the majority of people need more than 150 minutes per week of moderate PA to maintain a stable weight (less than 3% change in body weight), while clinically significant weight loss (at least 5% of body weight) may be achieved by a combination of adequate diet and moderate-intensity aerobic PA of 150–250 minutes per week (21,56,112-114). The ACSM recommends an initial goal of a reduction in body weight of 5% to 10% through a combination of moderate-intensity exercise and calorie restriction sufficient to produce a negative caloric balance of 500 to 1000 kcal per day (115). To prevent the regaining of lost weight, approximately 250 to 300 minutes of PA per week are needed (26).

PA and inflammation. Based on available research, the mode, intensity and duration of exercise required to optimize the anti-inflammatory effects cannot be established, and the mechanisms of these effects need to be elucidated. High training loads may be needed to maximize the anti-inflammatory effects of PA, but this may cause a small increase in infection risk (70). An independent contribution of an exercise-induced reduction in visceral fat, apart from other exercise-induced anti-inflammatory mechanisms, to reducing inflammation in adipose tissue, insulin resistance and risk of chronic disease also remains to be determined (70).

PA risks. PA confers risks as well as benefits, but it is important to recognize that regular activity of moderate or vigorous intensity is associated with an overall decrease in CVD events that far outweighs the transient heart risks associated with sporadic exertion (21). The absolute risk associated with a bout of moderate or vigorous physical activity is low and is on the order of 2 to 3 additional myocardial infarctions and 1 additional sudden cardiac death per 10 000 person-years of exercise (116). The risk is even lower among people who are habitual rather than sporadic exercisers.

It is very important to understand that the physiological and biochemical improvements that occur in the muscles, heart, and vascular function that occur with regular PA do not depend on an enormous physical effort, but rather on a physical effort that is greater than that to which an individual is accustomed. Brisk walking is generally recommended as the type of exercise that meets the criteria for moderate physical activity, but brisk walking may not be of sufficient intensity to meet the minimum criteria for moderate PA in a normal, healthy individual of college age, while it may be considered vigorous activity for someone older than 65 years. Thus, the dose of PA must be defined relative to an individual's age, physical condition and limitations, and gradual increases of training load should be performed in order to allow for bodily adaptation. Although athletes may require work at a high intensity to improve their fitness and performance, sedentary or relatively inactive individuals require little.

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CONCLUSION

Over the last decade, the quantity and quality of scientific literature on the relationship between PA and CVD have significantly increased. It is now known that exercise does much more than change traditional risk factors such as blood pressure, blood lipids, glucose tolerance and insulin resistance, metabolic syndrome, and overweight and obesity. PA also influences novel cardio-metabolic risk factors, endothelial function, haemostasis, inflammatory defence systems, the myocardium, and others. This means that even in the absence of positive changes in traditional risk factors, increasing the PA level can decrease the risk of CVD. Evidence from epidemiologic studies suggests that preventive effects of PA may be achieved by 150 minutes of moderate PA per week, while increases in the intensity and volume of exercise lead to further health benefits. However, although much progress has been made in this field, existing studies performed on human subjects do not clearly identify the type, intensity, and duration of exercise that are most beneficial to cardiovascular fitness and metabolic optimization. Information from athletes or patients is difficult to analyse due to the variability of human subjects and confounding comorbidities and medications. Animal (rat) models, in contrast, often allow for more invasive, extensive, and homogenous experimental designs than human models. These rat-based exercise studies may provide more information and help to elucidate the benefits of different training regimens to reduce the risk of CVD.

Acknowledgements

This work was supported by Junior Project 08/14 by the Faculty of Medical Sciences, Kragujevac, Serbia.

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