Physical activity is one of the most cost-effective treatments in medicine

The good and bad of exercise

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Summary

The 2016 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice have been recently published, with a large section addressing the benefits of physical activity on general health and control of cardiovascular risk factors. Regular physical activity remains the cornerstone of cardiovascular prevention and is recommended for the entire population. At least of 30 minutes a day of moderate activity 5 days a week or 20 minutes of intensive activity 3 days a week is recommended for the overall cardiovascular health, which is in line with the American Heart Association prevention guidelines. The prescription of physical activity is one of the most cost-effective treatments in medicine.

Keywords: cardiovascular prevention; cardiac rehabilitation; physical activity; lifestyle, sport cardiology

Introduction

The 2016 European Society of Cardiology (ESC) guidelines on cardiovascular disease (CVD) prevention in clinical practice have been recently published and include a large section addressing the benefits of physical activity on general health and control of cardiovascular risk factors (table 1) [1]. Regular physical activity remains the cornerstone of cardiovascular prevention and is recommended for the entire population. At least of 30 minutes of moderate activity per day 5 days a week, or 20 minutes of intensive activity 3 days a week is recommended for overall cardiovascular health, which is in line with the American Heart Association (AHA) prevention guidelines [2]. The prescription of physical activity is one of the most cost-effective treatments in medicine [3]. The World Health Organization (WHO) provided a road map to lower the burden of noncommunicable diseases for the period 2013–2010, mainly CVD, with the target of reducing the prevalence of insufficient physical activity relatively by 10% [4]. Sufficient physical activity is defined as meeting or exceeding 30 minutes of moderate activity five times a week or 20 minutes of vigorous activity three times a week, or equivalent [4].

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The benefits of physical activity are strong

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure [5]. Physical activity in daily life can be categorised into occupational, sport-related, conditioning, household, or other. Exercise is a type of physical activity that is planned, structured and repetitive with the objective to improve and to maintain physical fitness [5]. Sport is a type of individual or collective physical activity that involves respecting some prespecified rules in a game or competition, or for enjoyment.

The dose-response curve of physical activity and the reduction of cardiovascular risk is characterised by a huge decrease in subjects with light physical activity compared with those with sedentary lifestyle habits, followed by a flatter effect (inverse exponential) for those with heavy physical activity [6]. The maximal risk reduction was found at an exercise volume of 41 metabolic equivalents of task-hours (MET-h) per week, corresponding approximately to walking briskly (4.8–6.5 km/h) for 1 hour a day [6]. These findings underlie the importance of encouraging and recommending all sedentary subjects to start leisure physical activity, as 550 Kcal/week of energy expenditure was shown to decrease the relative risk of coronary heart disease by 12% and 1100 Kcal/week by 19% in a large meta-analysis [7]. Leisure-time running for 5 to 10 min/day even at slow speeds <6 miles/h (<10 km/h) was associated with a markedly reduced risk of death from all causes and CVD [8]. Regarding all-cause mortality reduction, running 5 min/day has a similar effect as walking 25 min/day (10% reduction), and running 25 min/day has a similar effect as walking 105 min/day (30% reduction) [9]. Even simply standing instead of sitting may represent a significant physical activity. In a large cohort of 221 240 individuals, those reporting longer standing times presented a lower risk of all-cause mortality. Compared with standing ≤2 h/day, hazards ratios (HRs) were 0.90 (95% confidence interval [CI] 0.85–0.95) for standing 2 to 5 h/day, 0.85 (95% CI 0.80–0.95) for standing 5 to 8 h/day and 0.76 (95% CI 0.69–0.95) for standing >8 h/day [10].

Improving physical activity habits consequently has an impact on aerobic capacity. Being fit with a high aerobic capacity was associated with a reduction of the risk of death. Subjects with an exercise capacity between 1.0 and 6.0 METs had a four- to five-fold higher risk of death compared with subjects with a capacity >13 METs [11]. In pooled data from six prospective cohort studies comprising 654 827 individuals, more leisure-time physical activity was associated with a longer life expectancy: a physical activity level of 01–3.74 MET-h/week (brisk walking 75 min/week) was associated with a gain of 1.8 (95% CI 1.6–2.0) years in life expectancy compared with no leisure-time activity (0 MET-h/week); higher levels (>22.5 MET-h/week, equivalent to brisk walking for >450 min/week) were associated with a gain of 4.5 (95% CI 4.3–4.7) years [12]. Finally, a meta-analysis reporting data from 102 980 healthy subjects showed that for each increase in cardiorespiratory fitness of 1 MET, the relative risk (RR) for all-cause mortality was reduced by 13% (RR 0.87, 95% CI 0.84–0.90) and for cardiovascular mortality by 15% (RR 0.85, 95% CI 0.82–0.88) [13].

In addition to the reduction of cardiovascular events, exercise has several positive effects on the control of blood pressure, diabetes, dyslipidaemia and weight. Further benefits have also been reported in other systems: (1) neurological, with reduction of anxiety, dementia, risk of stroke and improvement in cognitive function; (2) oncological, with decrease in the risk of prostate, breast and bowel cancer; (3) musculoskeletal, with decrease in the risk of osteoporosis, falls and disability [14]. Importantly, in this context it should be mentioned that all these data come from cross-sectional observational studies, where associations do not necessarily mean causality. Fitness has a strong genetic component and a person who is capable of doing 10 minutes of vigorous physical activity a day is not necessarily capable of doing 30 minutes a day to further reduce mortality [15].

“Bad” effects of exercise

The use of the term “bad” is of course provocative. For most patients treated in cardiac rehabilitation, concern about side effects of exercise is not a matter for consideration. According to the ESC prevention guidelines, activities that increase the heart rate up to 80% of the maximal heart rate (220 – age) can be considered safe [1]. In addition, no data suggest that activities leading to a heart rate 90% of the maximal can be unsafe for cardiac patients. For about 10 years, several groups regularly used high-intensity interval training in cardiac rehabilitation. Despite exercise intensities up to 95% of peak heart rate, a Norwegian study did not report any safety concerns compared with traditional continuous training in almost 5000 patients with stable coronary artery disease [16]. Even in patients with stable angina there is no evidence that exercise training beyond the ischaemic threshold is harmful [17].

Rarely, recreational or competitive athletes may die during or after an acute bout of exercise. There is now clear evidence that in the large majority of these cases exercise represents a trigger for arrhythmias in subjects with preexisting cardiac abnormalities (mainly hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy in young athletes and coronary artery disease in middle-aged athletes) [14]. In the prospective Registre des Accidents Cardiaques lors des courses d’Endurance (RACE Paris Registry), 73 life-threatening events (2 fatal) were identified in 511 880 runners; the majority of events occurred in experienced male runners (mean age 43 years), with no cardiovascular risk factors, atypical symptoms prior to the race or a negative treadmill test when performed [18]. Acute myocardial ischaemia was the most common reason and led to immediate myocardial revascularisation. Of note, all cases with an initial shockable rhythm survived. A meta-analysis of available studies suggested a low prevalence of life-threatening events (0.75/100 000) and that presentation with nonshockable rhythm (OR 29.9, 95% CI 4.0–222.5; p = 0.001) or nonischaemic aetiology (OR 6.4, 95% CI 1.4–28.8; p = 0.015) were associated with poor prognosis [18]. In the United States, the incidence rate of cardiac arrest among runners was estimated at 0.54 per 100 000 participants (95% CI 0.41–0.70); the incidence rate was significantly higher during marathons than during half-marathons and among men than women [19]. Cardiac arrests were commonly attributed to hypertrophic cardiomyopathy or atherosclerotic disease [19]. The incidence of sudden cardiac death varies markedly with age, regardless of sex or race [20]. The incidence of sudden cardiac is higher in black people (RR 1.3–2.8) and black people are more likely than others to present an unwitnessed arrest with a nonshockable rhythm [21]. Coronary artery disease was the principal diagnosis in the majority of men. In contrast, women had more nonischaemic heart disease than men, including dilated cardiomyopathy (19%) and valvular heart disease (13%) [22].

There is, however, much discussion in the literature on the possible side effects of chronic physical activity at extreme levels in athletes. This, of course, concerns a very specific subgroup of subjects regularly engaging in more than 10 hours of intense exercise per week. Cardiac adaptations in such athletes are characterised by electrical, structural and functional changes, such as sinus bradycardia, first degree atrioventricular

Table 1: Summary of the recommendations for physical activity in healthy adults [1].

Intensity	MET	Examples	% max. heart rate
Light	1.1–2.9	Walking <4.7 km/h, household work.	50–63
Moderate	3–5.9	Walking briskly (4.8–6.5 km/h), slow cycling (15 km/h) painting/decorating, vacuuming, gardening, golf, doubles tennis, dancing.	64–76
Intensive	≥6.0	Race-walking, jogging or running, swimming, singles tennis, heavy gardening.	77–93
Recommendations for physical activity			**Class/level**
For healthy adults, at least 150 minutes a week of moderate or 75 minutes a week of intensive physical activity.			**IA**
For additional benefits, gradual increase in aerobic physical activity to 300 minutes a week of moderate or 150 minutes of intensive physical activity.			**IA**

MET = metabolic equivalent of task

block, left ventricular hypertrophy, dilatation of the four heart chambers, and improved diastolic filling and stroke volume [14]. These changes can be considered to be physiological in most cases, since they seem to be reversible and without clinical consequences even in Olympic athletes followed for several years [23]. However, more recent data indicate that intense and regular exercise may damage a previously normal heart. It is now no longer debated that intense endurance training (>5 h/week) may cause a 5-fold increased risk of atrial fibrillation in middle-aged athletes compared with sedentary matched individuals, which is probably related to adverse atrial remodelling [14]. Although veteran orienteering runners were more frequently diagnosed with atrial fibrillation than the general population (5.3 vs 0.9%, p = 0.012), they were protected in terms of mortality (1.7 vs 8.5%) and coronary heart disease (2.7 vs 7.5%) [24]. In a very selected population of athletes, mainly professional cyclists, irreversible right ventricular remodelling associated with sustained ventricular tachycardia has been reported, leading to the debated concept of exercise-induced arrhythmogenic right ventricular cardiomyopathy [14]. Among 52 755 participants to a long-distance cross-country skiing event, a faster finishing time and a high number of completed races were associated with a higher risk of arrhythmias, mainly driven by atrial fibrillation and bradyarrhythmias, but no association was found for ventricular arrhythmias and no argument supported the concept of an exercise-induced arrhythmogenic right ventricular cardiomyopathy [25]. Finally, intense exercise may also have deleterious effects on peripheral vessels, with oxidative stress and shear forces that may induce atherosclerosis. Comparing 108 middle-aged long-term marathon runners with matched controls, Mohlenkamp et al. found higher coronary artery calcium scores and more cardiovascular events during follow-up in the marathon runners) [26]. In the Copenhagen City Heart Study with 1291 participants, subjects classified as strenuous joggers (>4 h/week fast pace) had no significant increased risk of mortality compared with non-joggers, whereas light or moderate joggers had a lower risk, suggesting a U-shaped relationship between all-cause mortality and dose of jogging [27]. However, several observational studies suggest that the longevity of men capable of prolonged vigorous physical exercise, such as Olympic medallists, is excellent and better that of the general population [28, 29].

Philosophical debate

Several philosophers made important statements on the positive effect of physical activity, although no clear recommendations with scientific data were available at the time. The importance of educating patients to perform physical activity was highlighted by Plato, the Greek philosopher: "In order for man to succeed in life, God provided two means, education and physical activity. Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise can save it and preserve it." Jean-Jacques Rousseau wrote "In every school a gymnasium, or place for physical exercise, should be established for the children. This much-neglected provision is, in my opinion, the most important part of education, not only for the purpose of forming robust and healthy physiques, but even more for moral purposes, which are either neglected or else sought only through a mass of vain and pedantic precepts which are simply a waste of breath." Emmanuel Kant pointed out that physical activity was useful for other performances of life ("An amusing lecture is as useful for health as the exercise of the body"), as did Thomas Jefferson for the quality of life: "Not less than two hours a day should be devoted to exercise, and the weather should be little regarded. A person not sick will not be injured by getting wet. It is but taking a cold bath, which never gives a cold to anyone. Brute animals are the most healthy, and they are exposed to all weather, and of men, those are healthiest who are the most exposed. The recipe of those two descriptions of beings is simple diet, exercise and the open air, be it's state what it will; and we may venture to say that this recipe will give health and vigor to every other description." Friedrich Nietzsche ("In every real man a child is hidden that wants to play") and Martin Heidegger ("We do not 'have' a body in the way we carry a knife in a sheath. Neither is the body a body that merely accompanies us and which we can establish, expressly or not, as also present-at-hand. We do not 'have' a body rather, we 'are' bodily.") suggested that the body was an entity that needs to be in movement for its survival and integrity.

There is no doubt that we forgot to cite other important philosophers. Interestingly, the 2016 ESC prevention guidelines used some population-based approaches very closed to the philosophical concepts mentioned above and summarised in table 2. The prescription of physical activity is, for the physician, probably more challenging than giving a treatment card for drug therapy, although prescribing physical activity is one of the most cost-effective medical interventions. In addition, physicians should deliver their message credibly, should use the roots of motivational interviewing or other behavioural interventions to improve lifestyle, and offer patients structured prevention programmes (e.g., cardiac rehabilitation). In addition, side effects of physical activity are not a matter of concern among physicians and patients, in contrast to drug therapy. However, physical activity may cause osteoarticular traumatic lesions, accidents or degenerative processes (e.g. osteoarthritis). To this purpose, we can quote Hippocrates: "Rest, as soon as there is pain, is a great restorative in all disturbances of the body."

Table 2: The 2016 ESC prevention guideline recommendations for population-based approaches [1].

1.	Government restriction and mandates (e.g., planning of towns or buildings).
2.	Media and education (e.g., media, programmes).
3.	Labelling and information (e.g., prescription, prompts).
4.	Economic incentives (e.g., taxes on cars, reduction of fitness fees).
5.	Schools (e.g., regular class rooms with physical activity).
6.	Workplaces (e.g., worksite fitness and protected time for exercise).
7.	Community setting (e.g., accessibility, aesthetic neighbourhood).

Interventions to improve physical activity

Strong evidence suggests that increasing physical activity should be a priority for clinicians and patients [3]. Our role is to encourage patients to be physically active and to perform activities integrating pleasure, happiness and self-confidence, without inflicting patients with dogma not driven by scientific evidence. To this purpose, interventions to improve patients' lifestyle habits have shown a benefit on clinical outcomes. In a Cochrane meta-analysis including a total of 63 studies including 14 468 participants with a median follow-up of 12 months, an exercise-based cardiac rehabilitation programme was associated with a reduction in cardiovascular mortality (RR 0.74, 95% CI 0.64–0.86) and the risk of hospital admission (RR 0.82, 95% CI 0.70–0.96) [30]. In addition, several domains of quality of life were significantly improved in patients attending cardiac rehabilitation [31]. The participation in well-structured cardiac rehabilitation after an acute coronary syndrome is recommended by ESC and AHA guidelines in order to modify lifestyle habits and increase adherence to treatment [2, 32]. This is especially true in patients with diabetes, as patient-centred care in multidisciplinary teams and based on shared decision-making and cognitive behavioural strategies are recommended to help patients achieve lifestyle changes [33].

A major challenge after participation in cardiac rehabilitation or in primary prevention is the ability to integrate physical activity into everyday life [34]. In the Geneva University Hospitals, we tested the effect of a pragmatic approach in the workplace [35]. A total of 63 participants were encouraged with use of motivational displays to use the stairs instead of elevators, and their physical activity monitored with a step counter. After 3 months of intervention, the metabolic profile significantly improved, with a reduction of low-density lipoprotein cholesterol levels by 20% and of insulin resistance by 25% [36]. Recently, we reported a significant decrease, by 20%, in proprotein convertase kexin 9 (PCSK9) levels in the same study, suggesting that physical activity can decrease PCSK9 level. These findings are clinically relevant given that PCSK9 has become a major and emergent therapeutic target for the prevention of CVD. In order to improve adherence to long-term lifestyle habits, we made several initiatives in Geneva to increase the attractiveness of our cardiac rehabilitation programme: (1) shortening the period from hospital discharge to the onset of cardiac rehabilitation (<10 days), (2) organising adequate follow-up from the hospital to the cardiac rehabilitation setting,

(3) offering free public transportation during the entire programme, (4) integrating activities, such as the use of electrical bicycles, into daily routine, and (5) targeting sporting challenges (e.g., the "Tour du Lac 2015" was a success, as in one weekend more than 30 patients known for a previous heart attack made the circuit of Lake Geneva by bicycle).

Another "Swiss made" initiative to support physical activity is the Swiss Tour du Coeur rally. Each year, a group of motivated and dedicated Swiss cardiologists travel to the ESC congress by bicycle. In 2015, 21 Swiss cardiologists started the trip from Basel, destination London, covering a total of 700 km in 7 days. Our research team was interested to assess metabolic changes within the timeframe of 7 days of intensive physical activity. We observed several positive modifications: low-density lipoprotein cholesterol levels decreased from 3.3 to 2.5 mmol/l ($p <0.001$), triglycerides from 1.1 to 0.7 mmol/l, fasting plasma glucose from 5.8 to 5.0 mmol/l ($p <0.004$) and insulin from 8.3 to 4.1 mmol/l ($p <0.001$). However, increases in cardiac biomarkers were also noted: the proportion of individuals with detectable high-sensitivity cardiac troponin (<3 ng/l) was higher after physical activity (57.1 vs 47.6%), as were levels of N-terminal prohormone of brain natriuretic peptide (NT-pro BNP: 66 vs 40 ng/l). A meta-analysis including 45 studies suggested that high-sensitivity cardiac troponin and NT-proBNP were prone to alterations due to strenuous exercise, and the addition of cardiac troponin in the detection of exercise-induced myocardial ischaemia seems modest compared with stress-testing plus myocardial perfusion imaging [37, 38]. The degree of inflammation was twofold higher after physical activity: C-reactive protein increased from 0.5 to 1.1 mg/l. Regarding urological safety, we did not observe traumatic prostatitis, but we did find a trend toward a decrease in testosterone levels, as expected in the acute phase of stress [39]. Due to the nonrandomised design, these changes cannot be directly linked to the effects of the 7 days of intensive physical activity. Mediation through inflammation, diet changes or other variations in electrolytes or hepatic function cannot be excluded. Ultimately, cardiologists and other healthcare professionals making the effort to attend the congress by bicycle can hopefully render lifestyle counselling more credible. By acting as role models to their patients, such cardiologists or primary care physicians can hope to positively impact on their patients' lifestyle behaviours, and thereby reduce CVD.

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