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Health-Related Beneficial Effects of Physical Activity

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MESTRE ALEXANDRE REBELO-MARQUES

PROFESSOR DOUTOR CARLOS ALBERTO FONTES RIBEIRO

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Artigo de Revisão Narrativa

Ana Filipa Costa da Cruz[1,2]
Alexandre Rebelo-Marques, MD, MSC[1,3]
Carlos Alberto Fontes Ribeiro, MD, PhD[1,4]

[1] Faculdade de Medicina, Universidade de Coimbra, Portugal
[2] afilipacruz97@gmail.com, Rua Dr Silva Pereira nº10, Varziela, 3060-215, Cantanhede
[3] alexrmarques@gmail.com, Azinhaga de Santa Comba, Celas, 3000-548, Coimbra
[4] fontes.ribeiro@gmail.com, Azinhaga de Santa Comba, Celas, 3000-548, Coimbra

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GLOSSARY

BDNF – Brain-Derived Neurotrophic Factor
BMD – Bone Mineral Density
BMI – Body Mass Index
CAD – Coronary Artery Disease
COPD – Chronic Obstructive Pulmonary Disease
CVD – Cardiovascular Diseases
HIIT – High Intensity Interval Training
IGF-1 – Insulin-like Growth Factor
IL-1ra – Interleukin 1 receptor antagonist
IL-1ß – Interleukin 1 beta
IL- 6 – Interleukin 6
MET – Metabolic Equivalents
mTOR – Mechanistic Target of Rifampicin
NK – Natural Killer
Th – lymphocytes T-helper
TNF-α – Tumor necrosis factor-alpha
WHO – World Health Organization

ABSTRACT

There is an overwhelming amount of evidence that supports the regular practice of physical activity as one of the major factors involved with reducing the risk of all-cause mortality and several medical conditions. Adopting a sedentary lifestyle is equally widespread and well established as a risk factor for the development of prejudicial health conditions such as chronic and non-communicable diseases. Based on this knowledge, this narrative review aims to evaluate the existing evidence on the numerous benefits of physical practice in everyone's life. Moreover, there are gains in the management of various prevalent diseases by having an active lifestyle. Exercise implies a wide variety of modalities and, each one has different benefits involving the body systems therefore depending on the outcome desired, there can be a best-suited training programme. It was considered relevant to elect exercise's benefits in the following areas: cardiovascular, respiratory, musculoskeletal, brain, psychological, metabolic, and immune system, whereby, in each topic, were discussed the impact of exercise physiologically and in some prevalent diseases. Furthermore, it was also discussed the influence of exercise in pregnant women and people living with cancer. Notwithstanding some shortage of evidence on understanding specific molecular mechanisms and the perfect exercise's posology in distinct circumstances, the main conclusion is the positive effect that physical activity has on the human body and in improving quality of life.

KEY-WORDS: Physical Activity; Exercise; Benefits; Health; Disease

RESUMO

Há uma quantidade esmagadora de evidências que apoiam a prática regular da atividade física como um dos principais fatores envolvidos na redução do risco de mortalidade e de várias condições médicas. A adoção de um estilo de vida sedentário está igualmente difundida e bem estabelecida como fator de risco para o desenvolvimento de problemas de saúde prejudiciais, tais como doenças crónicas não transmissíveis. Com base neste conhecimento, esta revisão narrativa visa avaliar as provas existentes sobre os numerosos benefícios da prática de exercício na vida de todos. Além disso, há ganhos na gestão de várias doenças prevalecentes por se ter um estilo de vida ativo. O exercício implica uma grande variedade de modalidades e, cada uma delas tem diferentes benefícios envolvendo os sistemas corporais, portanto, dependendo do resultado desejado, pode haver um programa de prescrição mais adequado. Foi considerado relevante eleger os benefícios do exercício nas seguintes áreas: cardiovascular, respiratória, músculo-esquelética, cerebral, psicológica, metabólica e do sistema imunitário, onde, em cada tópico, foi discutido o impacto do exercício, fisiologicamente e em algumas doenças prevalecentes. Além disso, foi também discutida a influência do exercício em mulheres grávidas e pessoas que vivem com cancro. Apesar de alguma falta de evidência sobre a compreensão de mecanismos moleculares específicos e a perfeita posologia do exercício em circunstâncias distintas, a principal conclusão é o efeito positivo que a atividade física tem no corpo humano e na melhoria da qualidade de vida.

PALAVRAS-CHAVE: Atividade Física; Exercício; Benefícios; Saúde; Doença

INTRODUCTION

Health was for a long time defined by World Health Organization (WHO) as a ‘’state of complete physical, mental and social well-being and not merely the absence of disease or infirmity’’. It has now evolved to be seen as a ‘’positive concept emphasizing social and personal resources, as well as physical capacities’’. (1)

Regular physical activity contributes to the prevention and treatment of several chronic diseases, as for instance, primary and secondary prevention of pulmonary and cardiovascular diseases (CVD; coronary heart disease, chronic obstructive pulmonary disease, hypertension), metabolic disorders (type 2 diabetes, dyslipidemia, insulin resistance, obesity), muscle, bone and joint diseases (rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, osteoporosis), several types of cancer (breast, lung, colorectal, prostate, gastric) and psychological illness (depression, anxiety). (2–4)

Regardless of the scientific evidence transparency about the gains to maintain a healthy lifestyle, several epidemiological studies continue to show impressive values on how the worldwide population remains fails to reach the minimum recommendations of exercise. (5) In 2019 more than 1.2 million deaths shall be attributed to physical inactivity (6) and, as a result of such impact of inactiveness makes this concern a public health problem. (7) Physical inactivity implies many serious consequences (obesity and increase risk of noncommunicable diseases). (5) To achieve a better quality of life, it is imperative to promote physical activity. Exercise is a simple, accessible, and affordable preventive/therapeutic plan as well as available to most of the population and must be intensified on a global scale. (8)

Over and above the several beneficial effects of exercise, it is, also, important to establish the contraindications so that physicians can prescribe it safely. These are based on the dosage (volume and intensity), frequency (sessions per week), type (aerobic or resistance), systemic and psychoactive effects. This way the prescription of physical activity is tailored to the individual. Exercise, such as every activity, does not exist free from risks. People should be aware of the contraindications to performing a specific exercise. (9)

An overview of Cochrane systematic reviews allowed to highlight the effectiveness of exercise in mortality rates reduction and improvement in quality of life. (2) Compelling cohort trials showed that the greatest risk reductions were noticed at the lower volumes of physical activity which indicates that simply changing from a sedentary to active life leads to a big improvement in health outcomes. Everyone benefits from becoming active and any activity is better than none. Newer evidence demonstrates that

the need to practice a minimum amount of physical activity to achieve health benefits may not be 100% true. (5)

In this review, we approach the general and specific health benefits of exercise in different body functions as well as its impact on prevalent diseases. The benefits should not be seen as isolated effects but overall effects accounting for the interaction between them. Additionally, will also be discussed the effect on specific populations, such as pregnant women and patients living with cancer.

MATERIALS AND METHODS

Research

For the development of this review on the beneficial effects of physical activity on the human body, the methods were used accordingly to the model used for narrative reviews and it was conducted an extensive literature search in the following databases: PubMed. It was done extensive research to look for articles which link exercise, benefit and the several areas chosen to evaluate as well as prevalent diseases. The research included articles until October 29th 2021 in English in a 12 year-range and were given more importance to systematic reviews, meta-analyses, and randomized controlled clinical trials. The search strategy used the Boolean operator AND and OR plus a key appropriate to each area and disease previously chosen. The key used for the search was the combination of (‘’exercise’’ OR ‘’physical activity’’) AND ‘’benefit’’ AND ‘’cardiovascular’’, ‘’respiratory’’, ‘’musculoskeletal’’, ‘’neurological’’, ‘’psychological’’, ‘’metabolic’’, ‘’immune’’, ‘’pregnancy’’, ‘’cancer’’. Furthermore, to improve and cover more detailed information about each chosen disease we conducted a new search combinating (‘’exercise’’ OR ‘’physical activity’)’ AND ‘’CAD’’, ‘’stroke’’, ‘’hypertension’’, ‘’heart failure’’, ‘’COPD’’, ‘’asthma’’, ‘’osteoporosis’’, ‘’rheumatoid arthritis’’, ‘’sarcopenia’’, ‘’Alzheimer’’, ‘’depression’’, ‘’diabetes’’, ‘’metabolic syndrome’’, ‘’lung cancer’’, ‘’colorectal cancer’’, ‘’breast cancer’’, ‘’prostate cancer’’. From this extensive research, the most relevant articles were first selected according to title relevance, followed by abstract pertinence and finally the ultimate reading to nominate the ones best suited to the focus of the present article. Ultimately, It was also consulted relevant references identified in the chosen articles as well as a reference to programmes of the WHO.

RESULTS AND DISCUSSION

Cardiovascular

The cardiorespiratory fitness can be considered predictor of CVD and all-cause mortality. (10) Higher cardiorespiratory fitness is associated with improved survival and reduced incidence of CVD and, improving exercise capacity is thus an important target to manage CVDs. (11) The effects of exercise on the myocardium and vascular system are dependent upon the frequency, intensity, and duration of the exercise itself and maintaining a regular physical activity is an important primary prevention for CVDs. (12)

Benefits of physical activity in the cardiovascular function are well known. It increases the function of vascular endothelium (10), decreases the inflammation marker (13), the risk of thrombosis (14) and coagulation (12) and improves lipid profile (10,15). This will lead to a deceleration of atherosclerosis process, which will reduce the risk of coronary artery disease (12) and ischemic stroke (16). In the other hand, physical activity is also responsible for the increase of insulin sensitivity (15,17), decrease vascular resistance (12) and sympathetic activity (18), and consequently achieve a negative energy balance. (19) With this in mind, we have a higher likelihood of preventing risks factors associated with CVDs, such as diabetes (20), hypertension (21) and obesity (19), that will decrease the risk of coronary artery disease, heart failure and stroke. (16)

Coronary artery disease (CAD) and stroke are two of the most important cardiovascular causes of mortality and morbidity worldwide. (16) Exercise when performed on a continuous basis has been proved to blunt angina's symptoms, improve myocardial perfusion and lower mortality in patients with both CAD and myocardial infarction. (12) A meta-analysis found that the equivalent of 150 min/week of moderate-intensity physical activity had a 14% lower CAD risk and those who engaged in the equivalent of 300 minutes/week of moderate-intensity physical activity had a 20% lower CAD risk, comparing to the inactive individuals. (22) Additionally, an updated meta-analysis displayed a reduction in cardiovascular mortality in patients with CAD as well as lower hospitalizations due to the disease. (23) Physical inactivity is an independent predictor of CAD and additionally exercise training has the potential to attenuate disease progression when at a symptomatic phase. (12) Hambrecht *et al* (12) compared percutaneous coronary intervention against regular physical exercise training in patients with CAD for 12 months to determine the effects of these interventions on symptoms, exercise capacity, myocardial perfusion and rate of hospitalization/mortality from disease complications. They recognize that patients in the exercise training group had an 18% higher event-free survival rate than those who underwent the coronary intervention isolated. Despite nowadays percutaneous coronary intervention is the first line treatment

for CAD, patients also benefit from an exercise program. (12) For stroke, a meta-analysis showed that individuals with low to high levels of physical activity have a reduction of 16 to 26%, respectively, in the risk of ischemic stroke comparing with sedentary individuals. (24) Likewise, it helps to maintain functional autonomy, decreases the risk of new cerebrovascular events, and encourages socialization when practiced in group in stroke survivors. (25)

Regarding elderly men, the most concerned population for CVDs, those who walked 1,5 mile/day were able to reduce 50% of the cardiovascular risk compared to those who walked fewer than 0,25 mile/day. (26) Even so, walking does not have an independent effect on CAD, it reflects an overall healthy lifestyle which includes a variety of behaviors such as nutrition as a more active pattern of living. (27) However, considering that regular walking is a more adopted and adhered exercise in elderly, it is a special important activity. One of the main predictors of exercise behavior is psychosocial factor of the patient. Their own confidence to engage in exercise is a big component of exercise adherence. (10) The major principle is that being as physically active as abilities and conditions allow it is better than none. Even small increases in moderate-intensity physical activity or replacing sedentary behavior with light-intensity physical activity could provide health benefits. (15,16)

Chronic hypertension is one of the most common risk factors for developing CVD. (18,21) Physical inactivity is a modifiable risk of hypertension as well as high body mass index (BMI), poor diet, smoking and alcohol consumption. (21) Modest levels have already a decrease in hypertension risk. (28) Nevertheless, more physically active people have lower high blood pressure prevalence. (21) This was evident, for instance, in the Henry Ford Exercise Testing (FIT) Project within a sample of more than 50.000 individuals was noticed that the ones who practiced higher levels of exercise, more than 12 metabolic equivalents (METs) had a 20% lower risk of hypertension compared to the ones who achieve only <6 METs. (11) There is a clear potential of increased physical activity in lowering elevated blood pressure and the prevention/attenuation the development of hypertension, so, accordingly, a structured exercise programme is a major recommendation in guidelines for nonpharmacological treatment of elevated blood pressure. (28) The greatest reduction in mortality can be assigned to more vigorous activities such as running. (21) The dynamic aerobic exercise has the most increased effect on lowering the blood pressure, but dynamic resistance and static isometric exercises have also benefitted. (28) Physiologically left ventricular hypertrophy is a complication to hypertension and, also, a strong predictor of this disease's prognostic. Reduction of the blood pressure typically leads to a regression of the hypertrophy and

improved prognostic, and, apart from pharmacological treatment, regular physical activity has shown to lower left ventricular hypertrophy in patients with hypertension. (29)

Several studies evidence that decreased cardiac respiratory fitness is associated with an enhanced in cardiac events. (11,12,30) Unfit individuals who improved their fitness status had a 35% lower risk of cardiovascular mortality compared with those who remained unfit. (11) With time, the progression of most CVDs will come to head of heart failure. There is a clear data about the association of lower physical activity and higher incidence of heart failure in elderly patients. (30) Regular physical activity is inversely related with chronic subclinical myocardial damage. (30) There is even evidence supporting an early mobilization of patients after a myocardial infarction and inclusion in exercise training programs very shortly after the insult. However, one of the problems of implementing exercise trainings is the lack of adherence and some physiological barriers like low energy or symptoms of heart failure. (10)

There is a wide-range choice of sports to practice and each one with several gains. While aerobic training has a better improvement of cardiorespiratory fitness, blood lipids profile and hemodynamics, resistance exercise might be more related to the glucose metabolism, increase in muscular strength and mass ad basal metabolic rate. (31) Football participation improves both aerobic fitness and cardiovascular function at rest as well as reduces adiposity among previously inactive adults. (17) Jogging and running have consistent findings to support their reduction in cardiovascular mortality and swimming practice is associated with lowering all cause and cardiovascular mortality risk. (17) When athletes engage in endurance events there are high blood concentrations of damage cardiac biomarkers in many of these specific population. The regular practice of vigorous exercise induces changes on the normal heart in order to promote the generation of a large and sustained increase in cardiac output. The development of athlete's heart implies adaptations that will affect the structure, electrical conduction, and function of the heart. And so, some athletes, in the process of aging, can reveal higher prevalence of atrial fibrillation, sinus node disease, second- or third-degree AV, ventricular arrythmias. (15)

Exercise-based cardiac rehabilitation is used as a secondary prevention in patients with CVD in order to improve their prognosis. Recent evidence has relied on high-intensity interval training (HIIT) to achieve greater improvements in cardiovascular fitness with the same safety when compared to moderate-intensity continuous training. The most used protocol for this population is long-interval HIIT which include 4 sets of high-intensity exercise with 4 minutes each interspersed with 3 sets of low-intensity, each lasting 3 minutes. A continuous 12-week practice of HIIT exercises improves respiratory

muscle function and within just 6-weeks there are also results in increased stroke volume, cardiac output, plasma volume and hemoglobin mass. One of the first cardiac changes in response to training is as improvement in resting heart rate which is an independent predictor of all-cause mortality. Although HIIT is a powerful approach to improve skeletal muscle total fiber amount and type proportions, capillary density, and metabolism markers in people with overweight/obesity (great risk factors for cardiovascular disease), there is less evidence on the effects of HIIT in the older population. (32)

Respiratory

Dyspnea, exercise intolerance and decreased health-related quality of life are transversal to chronic respiratory diseases. (33) Regular exercise can help improve the symptoms and physical function of patients with chronic lung conditions. For this subgroup of patients, becoming quickly out of breath can be daunting and they may not feel motivated to exercise. Avoiding exercise will be tempting, because they think it will make them breathless, but with less activity, less fit they will become, and daily activities will be harder. (33) To deal with shortness of breath, intermittent exercises are helpful. In this case, patients should alternate brief exercise with moments of rest (or slower exercise) which allows them to perform a greater amount of work. (33)

One of the most common chronic lung conditions is the chronic obstructive pulmonary disease (COPD), characterized by progressive airflow limitation, recurrent exacerbations, respiratory failure and premature death. (33) In fact, it is the third leading cause of death in 2019. (34) Pulmonary rehabilitation has the highest-level evidence on the therapeutic effect, since it alleviates symptoms like dyspnea and improves exercise tolerance. (35) These rehabilitation programme includes physical exercise, patient education and behavioral change which leads towards a more active life. A Cochrane review including almost 1500 patients, demonstrated that pulmonary rehabilitation after an exacerbation can decrease symptomatic phase (dyspnea) and ultimately enhance health-related quality of life. The physical exercise group also showed improvement in functional exercise capacity (assessed by 6-minute walk test) and physical performance. (36) The ultimate treatment goals in COPD is to reduce symptoms, disease progression, exacerbations and mortality as well as improve exercise capacity and overall health status. Physically active individuals are associated with lower risk of exacerbations, COPD hospital admission and all-cause mortality. (37) Specific exercise guidelines for patients with COPD are available in the literature. (35)

Asthma is a chronic respiratory condition that should not be physically restrictive. Many athletes have asthma and are able to compete at the highest level. (38) Children and adolescents are more frequently affected than adults. Physical exercise is safe and can be recommended in children with asthma. (39) The optimal cardiorespiratory fitness can be achieved through a 12-week aerobic training intervention in asthmatic individuals, with an intensity set at the personalized ventilatory threshold, which lead to a decrease in bronchial hyperresponsiveness and pro-inflammatory cytokines along with a significant reduction in airway inflammation. Moreover, the aerobic program reduce the occurrence of asthma-related symptoms, like shortness of breath, cough, wheezing and phlegm production and improve quality of life when compared to inactive peers. (40) A

recent systematic review of 11 studies showed that aerobic physical exercise reduces the prevalence and frequency of nocturnal symptoms in children and adults. (41) Accordingly, despite exercise could be a trigger for airways obstruction in asthmatics and provoking asthma-related symptoms, the consistent practice over time seam to build up tolerance to physical activity. (40)

Musculoskeletal

A key factor to the maintenance and balance of the musculoskeletal system is exercising. It can influence bone health both by preserving bone mass and strength and preventing the death of bone cells. (42) Likewise the importance of bone mineral density (BMD), the amount of muscle might also have a role in skeletal support. Muscle strength can be enhanced even when practicing exercise for a short period of time and it improves far much faster than the raise in muscle mass. (43) Physical activity is successful at opposing the decline in muscle mass and strength related with aging. One of the reasons is due to diminish age-related chronic inflammation. (44) The regular practice of exercise will increase muscle strength, coordination, and balance, and consequently an improvement in the general state of health. The bone's response is different depending on the type of exercise and even on the site. Strength training increases mechanical stress on the bone and further osteogenesis. There is undeniable evidence of its effect on femoral neck's, lumbar spine's, and radio's BMD but it does not appear to impact the whole-body bone mass. A multi-component practice with weight-bearing exercises like running and jumping can lead to osteogenesis and so increased BMD. Versatile movements and high peak load appear to improve bone accretion rather than repetitions successively. Aerobic intervention is not the best choice to induce changes in BMD, however, giving that it is a more accessible training method in older adults with a moderate effect in maintaining and slowing down the loss of bone mass, it should also be prescribed. If high impact aerobics activities such as stepping or jogging could be practiced safely, those are the preference as bone health concerns. Lastly, whole-body vibration has been used as prevention interventions of osteoporosis and bone fractures. It has great effects in stimulating osteogenesis, regardless of the duration of the programme. (45)

Physiologically when a young person exercises during his growth it causes changes in bone geometry which appears to increase bone strength and moreover bone mineral content. This leads to a higher peak bone mass throughout life. Nevertheless, being childhood and adolescence the most important periods of life to improve bone mass status, adults also benefit from loading to maintain bone mass, mechanical properties and reduce age-related bone loss. (43) Bone mass reaches its peak during the third decade of life, and after that, humans start to lose bone density. When someone is physically inactive and decrease the load on the skeleton it will result in a reduction of the BMD. This loss of bone density can be prevented with physical exercise, and the best ones are the weight-bearing kind, including weight training, walking, hiking, jogging, tai-chi and low-impact aerobics (46). This is relevant because the variation bone mass

and development of osteoporosis in senior people is mostly related to the peak bone mass. People who practice sportive modalities with higher overload provoked by the body weight or with higher utilization level of the muscular strength have a major bone mineral density. (42)

Regarding the long-term effect of exercise on bone mineral density and body composition in port-menopausal ex-elite athletes, high level of physical activity observed in female athletes can be related with the improvement in muscle mass, bone mineral density and bone mineral content. In addition, earlier physical activity (before menarche) seems to have a beneficial effect on bone mass and supports the prevention in bone loss due to aging. (43) Further studies in woman show better outcome of BMD on resistance training better in pre-menopausal woman whereas post-menopausal woman benefit more of a structured jump-training. (46)

Many bone diseases are associated with dysregulation of vascularization. Therefore, through exercise or mechanical loading there is a modulation of angiogenic mediators which are important to maintain skeletal health. (47) A paradigm of chronical bone diseases is osteoporosis, and it cannot be completely cured. However, there is a safe way to prevent the development of osteoporosis by exercising regularly. There is strong evidence that physical activity is a lifestyle factor which can improve the development of BMD. As engaging an active life can also improve bone structural outcomes, physical activity can hypothetically be seen as an ideal intervention strategy to improve musculoskeletal traits and reduce the incidence of fractures. (48) As exercise can focus on improving balance, gait and muscle strength, an exercise-intervention in older people used as co-therapy has been proven valuable to prevent falls in these higher-risk population and improve basal health status. (46,49) The majority factors for risk fractures are related with low physical activity, low BMD and frequent falls. (48) According to the fall risk calculated in 1 year long, about 97% of an older population would suffer / experience an incident compared to the control group. Plus, an exercise intervention is able to lower 23% of falls incidence. Intervention through exercise also reduces the number of people who suffer one or more falls in 15%. (49) Exercise can be seen as a therapeutic management for osteoporosis. However, as seen before, not all types of exercise affect equally BMD. Prescribing exercise in the elderly should be increasingly done along with the consideration to each vulnerability and capacity. Despite the lack of correlation to increase BMD, walking for at least 30 minutes a day seems to be effective to stimulate bone mass and manage a healthy. (50) Physical exercise should also be used as a non-pharmaceutical strategy to prevent fractures in postmenopausal women, a high-risk population for bone mass reduction. Considering

updated evidence both weight-bearing exercise and dynamic resistance training have clear benefits in enhancing spine and hip BMD for postmenopausal woman. (51) There is a worrisome about the osteoporosis' topic because of the fracture's incidence especially in elderly woman. These fractures imply a variety of complications which debilitate the patients' quality of life such as increase morbidity, mortality, rate of institutionalization and reduced autonomy. (46)

Rheumatoid arthritis is a chronic inflammatory joint disease which evolutes to cause great damage and significant disability and has an excess risk of cardiovascular disease itself. The big component of cardiovascular risk such as accelerated atherosclerosis can be compared to the one existing in diabetes. Physical activity has vascular benefits just as improved endothelial function and deceleration of the atherosclerotic process, so there might be favorable effects on bones. The effects of physical activity are numerous and ultimately culminate in decreasing of the disease's activity. Besides the specific improvements, it has also an impact on general health by increasing self-esteem, easing symptoms of depression, improving sleep quality, and decreasing pain perception. Despite all these gains, the reality is patients with rheumatoid arthritis tend to quite decrease exercise levels, given that the pain causes movement avoidance behavior and kinesiophobia. The unawareness of the beneficial effects of active behavior in rheumatoid arthritis leads patients to be sedentary. Physicians should educate their patients for the advantages of physical activity, such as aerobic activities and resistance training. Patient education can improve patient adherence as seen on different studies. Physicians must be conscious to these advantages as well in order to use exercise as a powerful therapeutical matter aside from pharmacological prescriptions. (52)

Lastly, the major change of exercise intervention is on physical performance. Physical frailty and sarcopenia can benefit from regular physical activity. Aerobic training and strength exercises on both upper and lower body adjusted to older people appears to improve muscle mass and muscle function. Protein intake has, also, an important role in maintaining muscle mass and it must be encouraged more powerfully in elderly. Due to ageing, they lack response in muscle protein synthesis and experience a reduction on post-prandial inhibition of muscle protein breakdown. So, logically, protein supplementation has positive effects on muscle mass gains even more during resistance-exercise. The dietary supplementation with more additional benefits was creatine which appears to have a synergetic effect with resistance training at specific muscle sites. (44,53)

Brain

There is a permanent connection between physical and cognitive function. When any of these functions are damaged it leads to a dependent life with increasing morbidity, disability, and frailty risk as well as mortality risk. Since exercise has potential effects to decelerate the normal decline of life, it can be a panacea for aging well. (54) Various important domains in healthy aging, from cognition to independent functioning and psychological/brain health were studied, and physical activity has benefits across all, particularly in aerobic exercises interventions. (55) Following a 6-month aerobic exercise intervention, researchers consistently demonstrate improvements in memory and execute functioning. In other randomized clinical trials, there are correlation between improvements in spatial memory performance and changes in hippocampal volume. (56) All exercise parameters are essential elements to the development of interventions program and must be considered in context of the overall goal. (57) Promoting multimodal exercise programs (aerobic training and resistance training combined) in older individuals over 60 years are great exercise recommendation because it impacts on both functional capacity and body strengths. (54) Exercise, is a promising and accessible low-cost treatment that is going to ameliorate brain functions without the undesirable side effects of medicines.

Exercise can so be referred as a non-drug method of preserving brain health and treating both neurodegenerative and psychiatric conditions. It can affect cognitive functions, spatial learning, and memory which are crucial for our evolution. Physical exercise, among other factors such as attention, mood or sleep-wake cycle, has the potential to influence the consolidation process and memory retention. It was further evidenced an improvement in short-term spatial memory in individuals with greater cardiovascular conditioning using aerobic exercise intervention. In addition, these cognitive findings were proportional to a volume enlargement of the left hippocampus. Studies have shown that both aerobic and resistance exercise are able to improve spatial learning and memory in humans. (58)

Nowadays, it is considered that our brain can exhibit persistent neuronal plasticity throughout all stages of life, which is responsible for the ability to learn new things, consolidate memories. The hippocampus is a region of the central nervous system with highly plastic characteristics, and it is associated to both spatial and declarative memory consolidation. There is an area of the hippocampus, the dentate gyrus, capable to generate new neurons and, from studies in rodents, it can double or triple in size after physical exercise. (58) Physical exercise-induced neuroplasticity may be related to the use of neurotransmitter, such as monoamines, neurotrophic factors (brain-derived

neurotrophic factor: BDNF) and also growth factors (insulin-like growth factor - 1: IGF-1) which act in the central nervous system. (58,59) Besides neurogenesis, neurotrophins' action like BDNF is a major modulator of brain plasticity and it appears to be the most sensitive to effects of exercise. It has action on the central nervous system but can also influence peripheral systems by reducing food intake, decreased blood glucose level, increased glucose oxidation rate and increased insulin sensitivity. It was once reported, in 1995, that voluntary exercise in rodents for 7 days could enhance the BDNF gene expression in the central nervous system. Regarding the grow factors, IGF-1 is responsible for maintaining brain cells and is also involved in differentiation, proliferation, synaptic plasticity, and neurogenesis. Positive associations have been reported between the cognitive function improvement and increased peripheral IGF-1 levels. There are different outcomes on IGF-1 levels regarding the type of exercise. Whereas resistance training is shown to increase blood levels, aerobic exercise does not seem to influence. However, it can enhance hippocampal levels of both IGF-1 and BDNF. Physical exercise is a power stimulant of angiogenesis in the brain. By analyzing cerebral blood volume in the dentate gyrus after 3 or 4 months of aerobic training in elderly and young subjects, respectively, it was verified an increase in the cortical hippocampal flow. On the contrary, sedentary subjects exhibited great number of vessel tortuosity in both brain hemispheres. Physical exercise seems to potentiate new neuronal generation and molecules such as BDNF and IGF-1 which promote exercise-induced neurogenesis. Studies in mice showed that, hippocampal plasticity may be induced by forced and non-forced physical exercise which increase neurogenesis, cell proliferation and dendritic branching. (58)

It is a fact that the quality of life in the major countries around the world is getting higher. With the increase of the quality of life, the population is also getting older (60), so, it is important to reduce the risk of physiological and brain linked disorders. Although older adults are the most affected by non-communicable diseases, they continue to be the least active age group and adopt a sedentary attitude during most of the day. Every healthy or non-healthy individual benefits from being active, but there should be a special focus on those who already have a mild cognitive impairment as this group is the one with the most risk for developing dementia. It is recommended by the WHO those older adults accomplished at least 75 minutes of aerobic exercise in vigorous-intensity, 150 minutes of aerobic exercise in moderate-intensity, or a combination of those above per week. (55) In elderly people, the hippocampus retracts, causing decrease in memory and dementia and positive effects of exercise have been reported on the hippocampus volume. Despite some previous findings that physical activity could improve hippocampus volume, a more recent theory is that exercise acts by attenuating the

neurodegeneration and neuronal mass decrease which is a component of aging. Since physical activity can promote retention of hippocampal volume and so mitigate cognitive decline, an intervention in the ageing population would have a great impact on public health. (59,61) It has benefits not only on mild cognitive impairment, dementia (55,57) and traditional cardiovascular risk factors but also anti-inflammatory effects which are involved in the pathophysiology of Alzheimer's disease. Giving that, evidence supporting the value of regular physical activity to prevent Alzheimer's disease or cognitive decline is growing. (59)

There is evidence that physical activity causes changes in functional brain network neural mechanisms in older population with or without cognitive impairments. (57) It is able to change brain structure or function which leads to outcomes and changes in behavior: with cognitive performance being the most evident. (56) Physical activity has a positive impact on physical and cognitive function. However, elder subjects show reduced responses following training when compared to the improvements of younger subjects. (54,58) There is an aging-dependent reduction in synaptic plasticity. (58) Furthermore, the ultimate effects of exercise on cognitive performance depends on physical and cognitive basal status. The healthiest older adults demonstrated the biggest effect sizes whereas frail older adults only manifest a mild cognitive impairment. (54)

In addition, individuals with higher levels of cardiorespiratory fitness or regular levels of physical activity have a better performance on different cognitive tasks, particularly those measuring executive or memory functions. Jonassen *et al.* (56) noted that individuals who at baseline had larger hippocampal volumes, were the ones to show greater improvements in cardiorespiratory fitness in response to a 6-month aerobic physical activity. Furthermore, individual differences such as physical functioning, mood, and cognitive functioning and specially brain structure have a predictive value in determining future engagement in regular activity. To engage an active life and practice exercise regularly, the brain itself is a major element responsible for adoption and adherence to a healthy behavior. An important predictor of physical activities related outcomes rely on adherence, enjoyability and likelihood of consistent exercise engagement. So, understandably, depressive mood is associated with worse cognitive performance, mainly in the areas of memory and executive functioning. The numerous and clear benefits of physical activity for preserving and enhancing public health are not at them maximal use when people still withstand to engage and maintain regular physical activity behavior. Beyond the effects exercise have on brain function there is now knowledge that health neuroscience and brain-body-mind mechanisms are important to change and improve health outcomes. (56)

Psychological

The psychological benefits in practicing low-intensity exercise transpire in all individuals, but especially in those who are untrained, the elderly and those who suffer from psychiatric disorders. Despite all the known gains of exercise, it is ultimately a personal experience as it concerns emotional effects. Both positive and negatives emotional effects of exercise have been reported. Generally, aerobic exercise when performed at an individual's usual level is noticed as a positive experience. People who voluntarily perform physical activity through the course of a normal day have the most positive experience. When exercise is executed at higher levels than participants' usual is less probably to improve mood and may even worsen it. Forcing people to engage intense exercise habits can have a negative effect such as decreased positive mood or increased negative mood. In this manner, spontaneous exercise habits are important to lower depression incidence. A more social activity appears to be a crucial element of exercise to improve depression. Furthermore, solitary exercise lacks that benefit, so social content within aerobic exercise seems to be a key element of treatment. (62)

Aerobic exercise accompanied counseling is more efficient in the therapy of depressive disorders than counseling alone. While clinical psychology aims to alleviate emotional symptoms of already occurred stressors, exercise training has the efficacy to also ameliorate stressors effects yet to occur. (62) Regardless exercise itself could act as a stressor, but it also can reduce the harmful effects of other stressors. (63) A 20 to 40-minute aerobic exercise has the potential to improve acute anxiety and mood meanwhile practicing at excessive levels can have a negative effect and lead to mood or behavioral disorders along with a decline of physical health. But the anti-depressive effects are not limited to aerobic physical activity. (64) Recent randomized clinical trials suggest there is a difference between the impact of aerobic and resistance exercises at psychological levels, regarding which symptoms it improves or even what anxiety disorders it can affect. Resistance exercise shows better outcomes in reducing signs or symptoms of generalized anxiety disorder, more than aerobic exercise. (65)

Physiologically, exercise leads to increase endorphin and serotonin levels and mitochondrial function. (64–66) It can also attenuate the hypothalamic-pituitary-adrenal axis response to stress. The endorphin hypothesis synthesizes a post-exercise euphoria, sedation and analgesia. Once 18 male runners with exercise addiction were submitted to a 2-week exercise withdrawal, they experienced an increase of symptoms of depression, fatigue, anger, and, on the other hand, decrease energy mood. When the exercise was resumed, there was an increase in endorphin levels and so improvement of symptoms. (64) Concerning mitochondrial function, it is important to neuroplasticity

and further poor mental health. New treatment for depression and mood-related disorders could be based on exercise effects in mitochondrial function by targeting dysfunction or enhancing function. An antidepressant effect can be achieved by enhancing mechanistic target of rifampicin (mTOR) signals which are increased by both voluntary and forced exercise and there is also a relation between mTOR signaling and improved mental health and cognitive function. About neurotransmitters, there are impairments in brain serotonin transmission that begin to be noticed with aging and are linked to depression in older people. Like pharmacological treatments such as selective serotonin reuptake inhibitors successfully manage depression because they work to prevent the reabsorption of serotonin and therefore increase their levels in the brain, exercise itself may also have a serotonergic effect and mimic the antidepressants. Finally, in diseases like depression and anxiety, there is evidence on hyperactivity of hypothalamic-pituitary-adrenal response to stress and exercise can attenuate it. As Inflammation contributes to mood disorders and poor mental health, exercise has an anti-inflammatory effect and so it can improve mental health outcomes in patients with inflammatory disorders. (64)

In 2001 depression was believed to be the leading cause of global burden by 2020. (67) Nowadays, the WHO estimate 280 million people worldwide suffer from depression, and as predicted it contributes greatly to the overall global burden of disease. (68) It has a 22% prevalence in the older community and living a sedentary life is significantly correlated to depression morbidity. (63) Anxiety disorders can be also associated with increased physical health risks. (65) In comparison to the general population, those who suffer from depression have reduced cardiorespiratory fitness. As it is a predictor of CVD and all-cause mortality, this vulnerable population is at risk of poorer well-being. Higher cardiorespiratory fitness should be promoted as a preventative strategy for this at-risk population on behalf of reduction future depressive episodes. (69)

Getting started in a youth age to practice exercise reflects on a more physically active adult which leads to physically and emotionally healthier lives. (70) People should notice exercise as a mental 'time out'. (64) Children might see physical activity as "playtime" and by doing so, it establishes an active mentality that can bring benefits throughout a lifetime. Hoshker *et al* (70) report that most benefits only become recognizable with 8 weeks of engagement in 45 to 60 minutes of physical activity each day and 3 to 5 days of vigorous aerobic activity. Participating in organized sports can provide more mental health benefits than practicing physical activity alone. Additionally, the enjoyment could be the key to both adherence to exercise and psychological benefits. (62)

There are still inconsistent findings on whether exercise has similar outcomes as antidepressant medications in literature. (64,65) As a result, the question remains: can exercise be more effective than pharmacological, psychological therapy, or therapeutical abstention in decreasing symptoms of depression? (66) What is known is traditional approaches to anxiety disorders are effective in reducing symptoms, however not every patient responds well to treatment. (67) Exercise-based interventions have been demonstrated to be effective in reducing symptoms of mental health diseases. (65) Plus, when is prescribed in combination with medication, it improves health outcomes significantly. (64,67) Accordingly, exercise plays an effective role in improving some mental health vulnerabilities and may be a crucial adjunctive treatment for psychotherapy. (64) In clinically depressed patients there should be a collaboration between conventional psychological treatment and exercise to improve outcomes. (62) Exercise would be a clear treatment choice, without the adverse effects of antidepressants and would allow to reduce polymedication in older adults. (66) For that reason there is an urgent need to have more evidence about the dose-response relationship between the type and technical features of exercise with specific disease effects. This matter will help to use structured physical activity as a basal prescription for every therapeutical management. (65)

Metabolic

We continuously need energy to maintain cellular and whole-body function. Through the synthesis of molecules (anabolism), and degradation of complex macromolecules (catabolism), energy consumption and energy production, our metabolism tend to maximize the energy use. (71) Exercise is a powerful modulator of metabolism. (72) Glucose is one of the major sources of metabolic pathways and while the brain needs about 100 to 120g of glucose per day to maintain a normal function, skeletal muscle increases its demand for glucose during exercise to maintain peak output. (71) The adaptations induced by exercise are particularly evident in cardiorespiratory musculoskeletal systems, body composition and metabolism. (73)

Regular practice improves glucose homeostasis and insulin sensitivity, control body weight, enhance lipid profiles, improve coronary blood flow, increase cardiac and endothelial function, reduce blood pressure, reduce systemic inflammation and delay age-related functional decline. (73–76) In 2020, the population with 60 years and over is slightly more than 1 billion people, globally, which represents 13,5% of the world's population. (77) The increase in life expectancy does not have been followed by good health conditions and so longevity leads to an increase in chronic diseases which progressively lessens physical and cognitive functionality. Since a big part of population is elderly, and there is a tendency to magnify those numbers by 2050, it is crucial to preserve proper body function at advanced ages. (74,77)

Diabetes is a very prevalent noncommunicable disease associated with insufficient exercise. The global prevalence of diabetes among adults has been on the rise and, only in 2019, it was estimated that 1.5 million deaths were directly caused by diabetes. (78) Diabetes mellitus can be classified into type 1, type 2, gestational or other specific types due to different causes. (79) While type 1 diabetes mellitus is caused by a defect of insulin secretion on account of autoimmune destruction of pancreatic beta cells, (76) type 2 diabetes mellitus has a multifactorial cause, and it is related to insulin secretory defects associated with inflammation and metabolic stress as well as peripheral insulin resistance. (79) About 90 to 95% of diagnosed diabetes are type 2 diabetes mellitus which is mainly due to age excessive body weight and physical inactivity. Most but not all patients are overweight, and this condition alone causes some degree of insulin resistance. Weight reduction may improve the diabetes in these individuals. Recent evidence with intensive diet combined with exercise intervention led to diabetes remission. (79) The American Diabetes Association recommends 150 min of moderate-to-vigorous physical activity per week, during 3 days a week at least with no more than 2 consecutives inactive days (80) Strong evidence highlights the major role of physical activity in improving weight control. Despite BMI is a useful measure used

transversely in research upon this topic, it does not distinguish fat of free-fat mass. (81) The most important component to reduce cardiovascular risk is the reduction of abdominal obesity which has anti-inflammatory effects. (73,75,81)

Metabolic syndrome is a complex condition and a cluster of cardio-metabolic risks like hypertension, dyslipidemia, insulin resistance and high waist circumference. Hence, this syndrome is a notable precursor to cardiovascular diseases and other chronic conditions. It is associated with sedentary lifestyles and individuals with lower cardiorespiratory fitness have a higher risk of developing metabolic syndrome. A prospective cohort study with more than 10000 individuals studied the BMI and lipid profiles during a 7-year physical activity intervention and was reported a dose-response between higher levels of exercise and improvement in serum lipid levels and BMI. After the 7 years, the metabolic profiles were increased comparatively to the sedentary group. A meta-analysis displayed the effect of aerobic exercise on cardiovascular risk among patients with metabolic syndrome without a diagnosis of diabetes and aerobic training seemed to improve waist circumference, cardiorespiratory fitness, diastolic blood pressure, HDL cholesterol, triglycerides, and fasting glucose. Additionally, a meta-analysis was conducted to determine the different outcomes in CVD and diabetes through physical activity intervention or usual care and observed a similarly effect in the exercise intervention group compared to the drug intervention for the secondary prevention of cardiovascular disease, prediabetes, and mortality. (75,82) Furthermore, there are a dose-relationship between physical exercise and cardiometabolic measures predominantly linear, which support the valuable in increasing levels of physical activity. (81)

Immune System

Exercise has positive and harmful effects depending on the degree of the activated responses of the immune system and more the duration of the physical practice. (83,84) Immune function may be improved if the activity is moderated, regular and above sedentary levels, however when is prolonged in a high-intense level, it can impair immune function. (83–85) Short and alone exercise session induce a transient response for 3 to 24h after the practice (83,86) and it may be responsible for increasing the risk to contract an infection. (84) The exercise stress may be involved in reactivation of virus. (83) Increased risk of post-race infections is positively related to pre-race infected episodes. There was an increased incidence of infections after race in runners with a previous race infection. Evidence that time of inoculation might be crucial for clinical outcome. Nieman *et al.* (87) reported the infection incidence after a Marathon in a large group of runners. In this study were compared the rates of infectious episodes after the race to the corresponding training volume before the race. It was reported the subjects with lower preparation had more risk of developing infections. There does not appear to be a relation between finishing time on the race and the incidence of infectious episodes. However, younger runners who achieve a faster finishing time when related to pre-race training status, could be a risk factor for developing post-race infections. The latter might be explained by exhaustion on the actual race which implies a larger strain on several physiological functions such as the immune system. Incidence of upper respiratory tract infections is higher on a large group of runners, who engage running mileage for a year. (86)

During exercise there are several modifications in the immune system. There is an increase in circulating leukocytes (mainly lymphocytes and neutrophils) and, to influence leukocytes' function, are more inflammatory cytokines in circulation like tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1ß) and acute phase proteins. Anti-inflammatory cytokines increase as well, interleukin-10 (IL-10), interleukin 1 receptor antagonist (IL-1ra) and interleukin 6 (IL-6), which, the latter, is secreted from contracted muscle fibers, acts as the initiator of the response as it induces IL-10 and IL-1ra and suppresses the production of TNF-α. The great elevation of IL-6, and anti-inflammatory cytokines during and after exercise can support the evidence that physical practice provides protection against the development of chronic diseases. (83)

It seemed that chronical training may cause polarization of lymphocytes T-helper (Th) into the Th2 phenotype and so predisposing elite-athletes to develop allergic disease and upper respiratory tract symptoms. Upper respiratory tract symptoms' prevalence was studied in marathon runners and compared to the general population.

Despite what is believed traditionally they may develop these symptoms as an allergic or inflammatory response rather than an opportunistic infection. (88)

Physical inactivity increases IL-6 pro-inflammatory response, the risk of infection and furthermore the prevalence of chronic non-communicable diseases. In the light of moderate practice there is an increase in IL-6 with anti-inflammatory effect, a decrease in risk of infection and chronic non-communicable diseases. With regular training the benefits strengthen without negative effects. However, when it comes to acute strenuous/elite sports there is a great risk of infection, a great elevation of IL-6 both pro and anti-inflammatory. (84)

Natural Killer (NK) cells are the most sensitive immune cell type to acute exercise and are mobilized within minutes of exercise. Maximal mobilization is achieved after 30 min of exercise. With prolonged exercise the max level can be maintained up to 3 hours, yet it does not improve more with time. It is still unclear if exercise change NK cells function or the count/distribution, or even modify functional capability. (85,89)

The combination of these exercise-induced mechanisms leads to a modification in cell mediated immunity and inflammation and as a result reduced risk of chronic disease but also increased risk of viral infection. Oral supplementation of vitamin C and E may attenuate the release of IL-6 and decrease cortisol response which would limit the exercise-induced depression of the immune system responsible for the higher incidence of infections. (83)

Pregnancy

Women are a high-risk group for weight gain which leads to cardiometabolic, reproductive and psychological health impacts. (90) Since pregnancy is a paradigm for behavior modification because of the increased motivation along with frequent access to medical supervision, women should be encouraged to adopt a healthier lifestyle. (91–94) During pregnancy, maternal physical activity maintains physical fitness, improves weight management, enhances the women psychological well-being, and reduces fetal morbidity (91,93,94) and further with a long-term mentality, it can lessen the prevalence of non-communicable diseases. (92)

Women, without contraindications to exercise (91,93,95), should maintain a physically active living throughout their pregnancy, avoiding activities with risk of injury and contact, preferring walking, swimming, yoga and overall low-impact aerobics. (93–95) Although 150 minutes per week of moderate-intensity prenatal exercise is strongly encouraged by clinical guidelines and worldwide health organizations, (92,93) more than 85% of pregnant women do not meet the recommendations for prenatal physical activity. (91,93,95) Practice of prenatal exercise is still related to some misconception and unnecessary fears. It may be sometimes regarded as not safe and that should be avoided during pregnancy. (93,95–97) Exercise is in fact safe and does not increase the odds of miscarriage or perinatal mortality, (96) prelabor rupture of membranes, induction of length of labor, caesarean section, vaginal tears, fatigue, musculoskeletal trauma or diastasis recti. (92,93,97) Acute and chronic prenatal exercise is well-tolerated by the fetus and does not adversely impact fetal heart rate or uteroplacental blood flow metrics. (98)

The greatest benefit of exercise during pregnancy is reducing gestational weight gain. Higher gestational weight gain is a risk factor for gestational diabetes, antenatal complications and can result in long-term obesity. (90,99) Mean weight gain can be decreased (94) mostly by a supervised exercise training combined with dietary intervention. (90) Non-active pregnant women are likely to increase more 18 to 23% the healthy weight gain (92) whereas women who undergo prenatal exercise interventions have a 32% reduction risk of excessive gestational weight gain. (94,97) Strong evidence demonstrate physically active women during pregnancy are nearly 25 to 30% less likely to develop gestational diabetes compared to their inactive peers. (92) Gestational diabetes complicates about 16% of all pregnancies (99) and is associated with fetal macrosomia (93) which predispose increased risk of obesity across life. In this manner, maternal exercise is associated with decreased risk of large and fatter neonates. (90) Despite the less likelihood of having a large-for-gestational-age newborn, there is no risk

of having a small-for-gestational-age newborn. (94) Moderate exercise is equally secure in the postpartum and lactation period considering does not affect breast milk quality or infant growth (92) and has positive effects as an adjuvant treatment of postpartum depression. (90) During pregnancy, more than 50% of women experience low back and pelvic girdle pain which is a debilitating condition. Although physical activity does not seem to reduce the likelihood of developing low back or pelvic pain, it decreases the severity during pregnancy and the early postpartum thus, this way, reducing the negative impact of this condition. (100) Physically active pregnant women are more likely to have a spontaneous vaginal delivery (91) and so have less demand in cesarean delivery, (92,94) that is, generally, associated with more adverse maternal and fetal outcomes thus delayed recovery. Prenatal exercise also reduces 24% the odds of instrumental delivery in the general obstetrical population. (97) Currently, there is still insufficient evidence on the effects and safety of prenatal exercise in the supine position, therefore, some caution when performing more intense acute bouts of exercise in the supine position is recommended. (93) Clinicians must also underline warning signs that will alert pregnant women to discontinue physical activity and seek help. (93,99)

Considering all this evidence, we can firmly assume that prenatal exercise is safe and should be recommended in pregnant women.

Cancer

Cancer is a generic term comprising more than two hundred different types of specific cancer-related diseases. It starts when there is an abnormal growth characterized by the transformation and multiplication of normal tissues into pre-cancerous lesions and subsequently into malignant tumors, that can spread to other body organs or regions, creating a secondary tumor or metastasis. (101) Cancer is the leading cause of worldwide death, and it is estimated that nearly 10 million deaths only in 2020 are due to cancer. (102) The most common cancer are the ones from the breast, lung, colorectal, prostate, skin (non-melanoma) and stomach. (102)

Around one third of deaths are due to behavioral and dietary risks, including high body mass index low fruit and vegetable intake, alcohol use, tobacco use and lack of physical activity (102,103), so cancer prevention relies, mostly, on lifestyle changes. (101,104) Physical inactivity has been associated with an increased probability of developing many different types of cancer. (101) Besides the preventive role of physical activity, there are consistent and strong evidence that it leads to reduction of tumor size (105), improves longevity among cancer survivors (101,105), decreases recurrence risk (101,104), cancer-specific and all-cause mortality (104,106) and has an impact on adverse effects of both treatments and cancer-itself. (106) Exercise is safe for cancer survivors and inactivity should be avoided, (107–109) so accordingly low cardiorespiratory fitness can be a great predictor of mortality. (103) At any point of the survivor journey, since the diagnosis until late stages, exercise helps to maintain and improve functional ability, body composition and quality of life. (107,108,110)

Increased levels of physical activity in prediagnosis or postdiagnosis are associated with improved survival outcomes for several types of cancer. (104,111) There is strong evidence on individuals with higher levels of physical activity having a 10-20% reduction risk of developing bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal and gastric cancers. (104) More active people before diagnosis have less severe forms of cancer (106) whereas post-diagnosis exercise has a greater effect on cancer outcomes, increasing cancer-specific mortality and coping with or recover from treatment. (105,111)

Patients with cancer should endorse in at least 2-3 exercise sets longer than 30 minutes (108,112) in a total of 150 weekly minutes of moderate-intensity physical activity or 75 weekly minutes of vigorous-intensity physical activity as recommended by WHO, international cancer and clinical groups. Which meets up to 10-15 MET hours per week (111) plus for every 15 MET hours/week increase in postdiagnosis physical activity there is a 16% reduction in cancer-specific mortality. (109) Physical activity should not be

started at full speed; it is important to engage slowly and have a gradual progression to increase both volume and intensity with time. (107) To deconditioned individuals, low intensity exercise has benefits and a positive impact on physical function and fitness. (113)

Supervised exercise interventions are the best modality to enhance beneficial effects on quality of life and physical function (110) along with starting a regular practice even during active treatment. (107) Combined aerobic and resistance training or moderate-intensity aerobic training are significantly effective in reducing fatigue, an important side-effect that can persist for years (106,113,114), anxiety, depressive symptoms, and overall quality of life. (107,108) Therapeutic exercise adjuvant to treatment may improve tolerance to cancer treatments and enhance functional outcomes. (106,113) Exercise when combined with chemotherapy had better outcomes than this method alone which support the theory it can act synergistically to increase treatment efficacy. (101) Moreover exercise during chemotherapy might be able to minimize treatment-related side effects, both short and long term and increase the ability of patients to physically tolerate greater dosages of treatment. (106,114) Aerobic capacity is an important indicator of physical fitness, and it can lower 10 to 33% over a 12-week period of chemotherapy. (107) The knowledge and understanding of cancer biology will ease the development of targeted exercise prescriptions, like dose, timing, type, to improve cancer outcomes. (109)

To these days, lung cancer is still the leading cause of cancer-related death worldwide. (102) Attributable to delayed diagnosis, lung cancer patients have about 18% 5-year survival rate, about 18%. (115) It is associated with symptoms from the disease itself but, also, many treatment-related, such as, pain, fatigue, sleep disturbance, shortness of breath, dry mouth, coughing, as well as psychological related distress which interfere with patients' daily life and further leads to physical inactivity and deconditioning. (115–117) Around 30% of lung cancer survivors suffer from anxiety and depression. Home-based walking interventions (40 minutes per session, 3 times a week) are effective in managing anxiety and depression in these patients and should be prescribed. (117) At least 30 minutes of moderate-intensity aerobic exercise for 2-3 days per week has shown to improve mood and health-related quality of life and reduce fatigue (108). In addition, moderate-intensity exercise programs can improve their aerobic capacity (peak oxygen uptake), muscle strength, functional capacity, anxiety level and emotional well-being. (118) Cardiorespiratory fitness levels are an independent predictor of survival rates, length of hospitalization (119) and lack of quality of life is, likewise, a factor of mortality among these patients (115). In this regard, exercise is beginning to be

seen as a potential adjuvant therapy. There is an evident time-window between lung cancer diagnosis and the surgery intervention and, according to Bhatia *et al.* (119) recent findings, if a patient is submitted to an 8-session program of HIIT enhances his physical condition and consequently better outcomes after surgery. During this preoperative waiting period patients improve their aerobic and exercise capacity by 15% plus resting heart rate, recovery heart rate and dyspnea. HIIT lowered about 45% of pulmonary complications, mainly atelectasis. On the other hand, Messaggi-Sartor *et al.* (116) reported that patients who underwent lung resection in the previous 6 to 8 weeks were submitted to an 8-week exercise program of aerobic and high-intensity inspiratory and expiratory muscle training had significantly results of increased exercise capacity and also respiratory muscle strength. After lung resection, patients who commonly have already a poor physical fitness can worsen their basal state. High-intensity endurance and strength training is well tolerated and is able to, primarily, improve peak oxygen uptake and further enhance muscular strength, total muscle mass, functional fitness, quality of life. (120) It would therefore be interesting to combine a pre-rehabilitation HIIT regime with a post-operative rehabilitation programme.

Breast and endometrial cancer are some common cancer types in women. Each year, there are around 2,3 million new cases of breast cancer in the world. (102) Physical function is one of the predictors survival and mortality in breast cancer survivors. Even moderate daily activities are associated with survival improvements on advanced breast cancer patients. (121) Aerobic and resistance combined intervention produced the greatest benefits for patients and were also linked to improved metabolic syndrome, sleep quality, cancer-specific quality of life and muscular endurance of the superior upper and lower body. (121–126) A psychological evaluation of mood alterations, spiritual or social distress may be crucial to improve exercise adherence and minimize patient's fear, anxiety, and depression towards their disease. (124) Fatigue is a common impact in breast cancer survivors that affects approximately 40 to 80% of this population when undergoing active treatment. It can affect lives even following the therapeutic treatment and so it can be believed as a strong predictor of lower survival rate. When compared with conventional care, supervised exercise appears to have a favorable effect on cancer-related fatigue. Besides being considered a safe therapy in fatigue management it also improves psychological and physical outcomes. (126) About 20% of breast cancer patients during their treatment course may develop lymphedema which is an incurable and chronic disease with great impact in people’s lives. Resistance training helps to maintain or regain physical function of the affected arm along with improving body composition. (123) Regarding the endometrial cancer, obesity is a well-established risk factor. Furthermore, a study including more than 50,000 Norwegian women, increasing

the levels of physical activity was associated with a 21,9% lower incidence of endometrial cancer in women independent of BMI. (127)

The best impact of physical activity is seen in colon cancer more than for rectal cancer. (128) There is strong evidence that physically active individuals have a 19% less risk reduction of developing colon cancer (104) and, on the contrary, prolonged time sitting has a 30% higher risk of developing colorectal cancer. (101) Furthermore, people who practice prediagnosis physical activity regularly have a 19% decreased risk of mortality and 15% reduced risk of cancer-specific mortality compared to those with lowest levels of physical activity. Beyond improving mortality rates, prediagnosis physical activity can enhance tolerance of treatment and lower risks about comorbid conditions. The risk associations, concerning postdiagnosis physical activity, are about 36-37% for total and cancer-specific mortality. The inverse relations between the regular practice of physical activity and improved outcomes crosswise different populations and both sexes. There is a significant dose-response relationship observed between pre- and post-diagnosis and enhanced outcomes, which highlights the need to practice more exercise. (128) Besides the beneficials of aerobic and resistance exercise in improving functional capacity, there is no adverse events reported following strength and endurance training interventions. Indeed, endurance and interval training with progressive increase of loading seems to be the most effective to enhance functional capacity. (129) Some of the physiological mechanisms that can explain this reduced risk are reduction of plasma levels of insulin and IGF-1, that usually when in high levels are associated with tumor progression, metastatic disease, and decreased survival time. On the other hand, sedentarism increases levels of chronic inflammation which is related to cancer progression and metastasis. Lastly, physical activity has a protective role over mortality rates independent of other factors like smoking, tumor stage or receiving treatment. (128)

Prostate cancer is the most frequently cancer among males worldwide. (130) There is moderate evidence for reduction of associated mortality in 38% (104) and decreased 57% risk of prostate cancer progression in physically active individuals. (131) There are consistent findings about physical activity, particularly in vigorous intensity exercise, when performed in early adulthood may be associated with a lower risk of prostate cancer. (130,132) Vigorous practice is required to achieve a maximal effect (132) and its mainly evident for advanced prostate cancer. The population with highly active lifestyle appears to have less prevalence of tumors with a high Gleason score and decrease risk of mortal cancer. For each additional 30 minutes of exercise, the risk of prostate cancer decreases some 8%, when comparing to those that performed less than 30 minutes of walking or cycling a day. (133)

Regarding the esophagus cancer, a systematic review shows that the incidence risk can be reduced in 21% in physically active individuals, when compared to less active. Gastric cancer has strong evidence on greater amounts of physical activity are related to decreased risk of incidence. Furthermore, there is a dose-response relationship with increased levels of exercise, lessens the risk of gastric cancer. (104)

CONCLUSION

The presented work highlights a great amount of qualified evidence regarding the health-related beneficial effects of physical activity and exercise on general health and on preventing and/or treating noncommunicable diseases. We can firmly conclude that exercising is clearly beneficial. Allied to the current longevity of the world population, physical activity is cornerstone to promote a healthy aging, while maintaining a reasonable health-related quality of life. It remains necessary to increase awareness on the benefits of physical activity to overcome barriers to exercise, such as the lack of motivation and time. The next step is to define and individualize exercise according to each disease and intended goal so we can achieve the best potential.

Health professionals must be able to educate and create better conscientiousness around patients, as well as to prescribe exercise safely as medicine. The exercise prescription for the general population, without illness, requires moderation and observation of the physiological principals of physical exercise. On the other hand, for the populations with special conditions, there are specific guidelines, that with the appropriate supervision allow a safe practice of the exercise, controlling for and reducing the associated morbidity.

Exercise should always become part of a healthy lifestyle and act as a polypill for prevention and coadjutant treatment of noncommunicable diseases. With so many benefits, practicing physical exercise should be a no-brainer. There should not be any excuses to not remain active and enjoy the advantages of all the many health-related benefits of physical activity.

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