

TOPICAL REVIEW

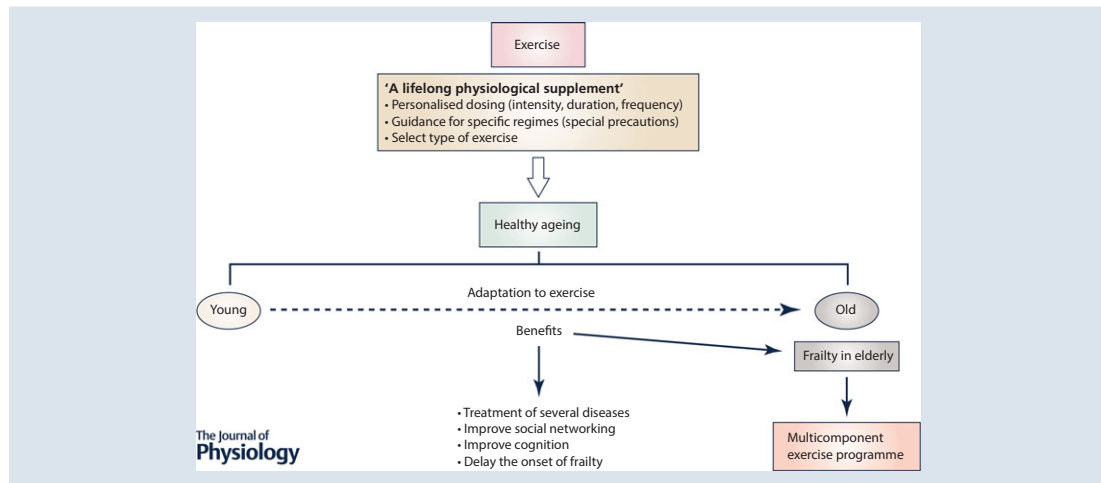
Exercise: the lifelong supplement for healthy ageing and slowing down the onset of frailty

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Abstract The beneficial effects of exercise have been well recognized for over half a century. Dr Jeremy Morris's pioneering studies in the fifties showed a striking difference in cardiovascular disease between the drivers and conductors on the double-decker buses in London. These studies sparked off a vast amount of research on the effects of exercise in health, and the general consensus is that exercise contributes to improved outcomes and treatment for several diseases including osteoporosis, diabetes, depression and atherosclerosis. Evidence of the beneficial effects of exercise is reviewed here. One way of highlighting the impact of exercise on disease is to consider it from the perspective of good practice. However, the intensity, duration, frequency (dosage) and counter indications of the exercise should be taken into consideration to individually tailor the exercise programme. An important case of the beneficial effect of exercise is that of ageing. Ageing is characterized by a loss of homeostatic mechanisms, on many occasions leading to the development of frailty, and hence frailty is one of the major geriatric syndromes and exercise is very useful to mitigate, or at least delay, it. Since exercise is so effective in reducing frailty, we would like to propose that exercise be considered as a supplement to other treatments. People all over the world have been taking nutritional supplements in the hopes of improving their health. We would like to think of exercise as a physiological supplement not only for treating diseases, but also for improving healthy ageing.

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Abstract figure legend Exercise is a physiological supplement not only for treating diseases but also for improving healthy ageing.

Introduction: the London bus study on exercise and health

The favourable effects of exercise on health are now well accepted (Pedersen & Saltin, 2006). The situation, however, was very different in 1953 when one of the most important studies on exercise was first published: this was the London bus study performed by a London epidemiologist, Dr Jeremy Morris (Morris *et al.* 1953). Dr Morris analysed data on cardiovascular disease and its relationship with physical activity, showing a remarkable difference in cardiovascular disease between drivers of the famous double-decker buses and the conductors. The conductors were at approximately half the risk of dying of cardiovascular disease when compared with the drivers. Dr Morris and his team observed the conductors' behaviour in their daily activity and found that they would typically climb approximately 500–700 steps per day. This is a substantial amount of physical activity.

Even though stress may be a confounding factor, the all-important publication of Morris and co-workers in *The Lancet* in 1953 became a critical landmark in fostering interest in the field of physical exercise and its beneficial effects (Morris *et al.* 1953).

The hypothesis that physical activity promotes health and longevity is not new. In Graeco-Roman times Hippocrates, and later Galen, recognised the need for promoting and prescribing exercise for health-related benefits (Vina *et al.* 2012) but they had no scientific

evidence. Dr Morris performed systematic research that brought to light the whole field of physical activity epidemiology. Subsequently, many other investigations have shown that exercise is good for health. Further on in this review we will describe how exercise can be considered as a treatment for diabetes, osteoporosis, depression and several other diseases (Vina *et al.* 2012).

We recently suggested that exercise is a powerful intervention that acts as a drug (Vina *et al.* 2012). Our views on this point will also be discussed.

Exercise and lifespan: primary and secondary ageing

John O. Holloszy described two types of ageing: the first is primary ageing, which is 'an inevitable deterioration of cellular structure and function independent of disease and environment' (Holloszy, 2000). Slowing down primary ageing increases maximal lifespan in many species. There is no intervention able to reverse primary ageing in humans (Booth *et al.* 2011). Genetic factors are thought to be responsible for maximal longevity of any given species. To date, hundreds of genes connected with ageing and longevity have been identified (Sinclair & Guarente, 2006). Most of these genes perform functions that maintain cells, such as repairing damage to DNA or regulating anti-oxidant levels (Stewart, 2014). Individually, genes have a relatively small impact on lifespan, but together they account for 25% of our longevity (Stewart, 2014) (see Fig. 1).

Secondary ageing is ‘caused by diseases and environmental factors such as smoking and exposure to ultraviolet radiation’ (Holloszy, 2000). Secondary ageing alters life expectancy (average length of life in a population), but not maximum lifespan. More than 70% of people over 65 have two or more chronic conditions, such as diabetes, arthritis, cancer, stroke, or heart disease (Hung *et al.* 2011; Fontana *et al.* 2014). Delaying one age-related disease probably staves off others (Fontana *et al.* 2014). This aspect of ageing may be influenced through a lifetime of physical activity (Stewart, 2014) (see Fig. 1).

However the characteristics of exercise (intensity, duration, frequency, type of exercise) for extending lifespan are far from clear. Moreover several interspecies differences have been reported (Garcia-Valles *et al.* 2013). Exercise has been associated with a slowing of age-specific mortality in rats, and with increased median lifespan (Holloszy *et al.* 1985). However, contradictory results have been reported in mice (Samorajski *et al.* 1985; Navarro *et al.* 2004). Lifelong spontaneous exercise does not change either average or maximal lifespan in mice (Garcia-Valles *et al.* 2013). These discrepancies may be explained by different experimental conditions, such as type of exercise or age of the animal at the onset of intervention, among others (Garcia-Valles *et al.* 2013).

The ideal ‘dose’ of exercise for improving longevity in humans is also uncertain, but data support an inverse association between regular exercise and mortality. In longitudinal studies, physically active men and women have an approximately 30% lower risk of death compared

with inactive people (Schnohr *et al.* 2015). No upper threshold for physical activity has ever been recommended (Pate *et al.* 1995). In fact, in studies performed on top-level athletes, participation in endurance competitive sports increases life expectancy (Hartley & Llewellyn, 1939; Prout, 1972). Moreover, Karvonen and co-workers found that Finnish champion skiers lived 2.8–4.3 years longer than the general male population in Finland (Karvonen *et al.* 1974). We tested the effect of strenuous exercise, performed by well-trained humans, on their longevity. We measured average and maximal lifespan in cyclists who had taken part in the Tour de France between the years 1932 and 1964 and compared them with those of the average population in those years. Only cyclists born in Belgium, France and Italy were included in our study. The results were striking: we found an 11% increase in average longevity in Tour de France participants when compared with the general population (Sanchis-Gomar *et al.* 2011). These results have been confirmed recently with the observation of a significant 41% lower mortality rate among French elite cyclists from the Tour de France, compared with the general male population (Marijon *et al.* 2013). Evidence from human studies supports the notion that regular, vigorous aerobic exercise might be a useful tool, with a dose–response effect, to improve the overall health status and longevity of the general population (Ruiz *et al.* 2010; Teramoto & Bungum, 2010). However, the controversy regarding the potential adverse effects of regular strenuous physical exercise continues (Benito *et al.* 2011; Schnohr *et al.* 2013). Schnohr and co-workers have found that

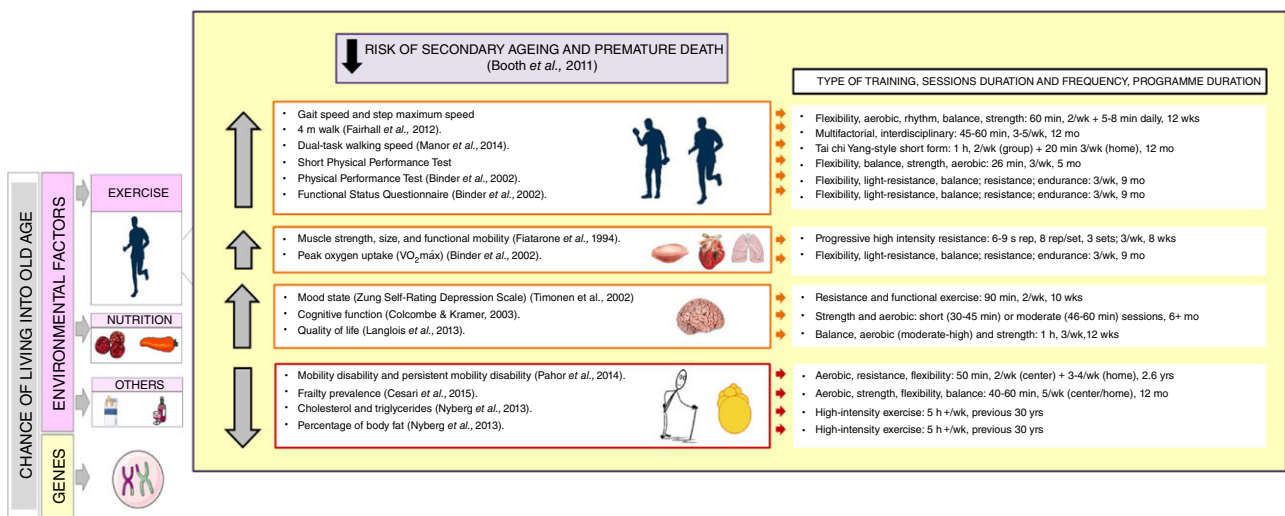


Figure 1. Factors that are involved in the chances of living to old age
 Exercise is an environmental factor that increases lifespan and healthspan by decreasing the risk of secondary ageing and premature death. The longer-term changes in the organism related to the adaptation to exercise in older persons is the delay in the onset of frailty (Fiatarone *et al.* 1994; Binder *et al.* 2002; Timonen *et al.* 2002; Colcombe & Kramer, 2003; Booth *et al.* 2011; Fairhall *et al.* 2012; Langlois *et al.* 2013; Nyberg *et al.* 2013; Gine-Garriga *et al.* 2014; Manor *et al.* 2014; Cesari *et al.* 2015).

moderate-intensity joggers have lower mortality rates than sedentary people or high intensity joggers. In other words the relationship between intensity of jogging and mortality follows a U-shaped curve (Schnohr *et al.* 2015). Thus, the ideal 'dose' of exercise needed to improve longevity is not a simple linear relationship. Genetic aspects as well as lifestyle factors (smoking, diet and alcohol consumption) may be important in interpreting studies aimed at determining the effect of exercise training on longevity.

It is also relevant that training-induced adaptations vary considerably between individuals. In the HERITAGE Family Study it was shown that there are two groups of persons in relation to the different health parameters associated with exercise: responders and non-responders (Bouchard & Rankinen, 2001). Several previous studies have shown that a proportion of subjects demonstrate little or no improvements in $\dot{V}_{O_2 \max}$, maximal work rate, submaximal exercise heart rate, submaximal respiratory exchange ratio or insulin sensitivity despite regular endurance training (Prud'homme *et al.* 1984; Skinner *et al.* 2001; Boule *et al.* 2005; Hautala *et al.* 2006; Scharhag-Rosenberger *et al.* 2012). The degree to which $\dot{V}_{O_2 \max}$ improves in older people with training is also variable (Kohrt *et al.* 1991). Timmons *et al.* (2010) identified 11 single-nucleotide polymorphisms that together explained 23% of the interindividual variance in training-induced $\dot{V}_{O_2 \max}$ changes, corresponding to about 50% of the estimated genetic variance for $\dot{V}_{O_2 \max}$.

From increases in longevity to healthy ageing: the concept of frailty

A vast increase in average lifespan of different populations has occurred worldwide in the 20th century, especially in developed countries. Indeed, the average lifespan in Spain in 1900 was around 30–35 years and in 2000 it was approximately 83–85 years (Garcia-Valles *et al.* 2013). This enormous increase in average longevity has occurred due to the development of public health systems (prevention of disease), nutrition and clinical medicine.

In the last three decades, an enormous effort has been put into understanding the biological bases of ageing (for a recent review see Lopez-Otin *et al.* 2013), and many laboratories have endeavoured to increase longevity in animals by genetic manipulation as well as by 'lifestyle improvements' (Matheu *et al.* 2007; Borras *et al.* 2011). The concept of longevity-associated genes was coined around 20 years ago to describe genes that when upregulated in an animal resulted in an increase in lifespan (for a review see Sinclair & Guarente, 2006). Antioxidant genes, p53, telomerase and the IGF receptor are all proteins that are encoded by longevity-associated genes whose modulation has resulted in significant increases in

lifespan in animals (Vina *et al.* 2013a). However, in the last 10–15 years, emphasis has changed from increasing average and even maximal longevity to promoting healthy ageing (Garcia-Valles *et al.* 2013; Vina *et al.* 2013b). The idea is to provide guidelines for the population to reach a lifespan that is closer to the maximum while also improving health and happiness.

As lifespan increases so the concept of frailty has emerged. Age-associated frailty is a clinical syndrome that leads to a lowering of biological reserves, due to poor regulation of physiological systems, that results in an individual being at risk, especially when facing minor levels of stress. It leads to poorer outcomes in terms of disability, hospitalisation and early death (Fried *et al.* 2001; Ingles *et al.* 2014; Rodriguez-Manas & Fried, 2014). The prevalence of frailty in the elderly approximates 15%.

There are two important characteristics of frailty: firstly if left unaddressed it will evolve into disability and eventually death, and secondly, if treated the onset of frailty can be delayed. Notably, analyses by the European Union have shown that by the year 2020, approximately half the population over 70 years of age will be at high risk of disability. Prevention of disability is obviously a major medical and social concern (Rodriguez-Manas & Fried, 2014). Exercise is one of the most important interventions to delay the onset of frailty (Casas Herrero *et al.* 2015).

The number of studies analysing the effects of exercise on frailty is still relatively small (Binder *et al.* 2002; Chin *et al.* 2008; Daniels *et al.* 2008; Theou *et al.* 2011; Chou *et al.* 2012; de Vries *et al.* 2012; Clemson *et al.* 2012; Freiburger *et al.* 2012; Cadore *et al.* 2013). The general consensus is that exercise is the most successful way to delay the onset of frailty (see Fig. 1). Of the various types, multicomponent exercise is the most effective. This intervention includes resistance, balance, endurance and coordination training (Cadore *et al.* 2014). However, at present we lack a multicomponent exercise programme that can be stratified to protect against frailty-associated problems and also social and cognitive aspects to enhance the quality of life in older individuals (Rodriguez-Manas & Fried, 2014).

Significant efforts are being made worldwide to establish a suitable exercise programme. Another key question is whether personalised exercise and nutrition, in particular foods with high protein, mineral and vitamin content, can act synergistically to delay the onset of frailty.

In the context of this review focused on the benefits of exercise on healthy ageing, it is noteworthy that the LIFE Study shows that exercise reduces the incidence of major disability in ageing. Importantly, we propose that exercise should be viewed in terms not only of delaying the onset of frailty but also of contributing to cognition and social networking (Pahor *et al.* 2014).

Responses and adaptations to exercise in ageing

Hawley and co-workers recently provided evidence that the capacity of humans to exploit endurance and thermo-regulation enabled early East Africans to succeed as game hunters (Hawley *et al.* 2014).

Short-term responses to exercise refer to changes in parameters in an organism that occur almost immediately after initiating exercise, whole-body oxygen uptake increasing about 20-fold during maximal exercise, heart rate increasing up to 200 beats min^{-1} and ventilation increasing up to maximum of around 150 L min^{-1} (Saltin & Astrand, 1967; Hawley *et al.* 2014). Whole-body metabolism responds to exercise by increasing muscle glucose uptake, glycogenolysis, and ATP turnover (Monleon *et al.* 2014). Skeletal muscle is central in the response to exercise with dramatic changes in metabolism including active glycolysis, turning muscle into a tissue that produces large amounts of lactate, increasing glucose and oxygen utilisation, and CO_2 production (Hawley *et al.* 2014). In addition to conventional metabolites a large number of myokines with profound signalling consequences are also released from muscle (Febbraio & Pedersen, 2005).

Adaptation to exercise refers to longer-term changes in the organism to prepare it for subsequent exercise. We have recently measured characteristics of the adaptation to exercise in older sedentary and active individuals aged 60–65 years and compared them with individuals aged approximately 20–25 years. We found an important change in body composition between young and old subjects; the younger had 17.7% of body fat whereas individuals aged 60 with the same height and body weight had significantly higher body fat of 26% (Nyberg *et al.* 2013). Notably, if older individuals had performed endurance exercise (5 h per week for the past 30 years), they maintained their percentage of body fat at even lower levels than the young sedentary individuals, i.e. 15%. The $\dot{V}_{\text{O}_2\text{max}}$ of young individuals was 3.6 L min^{-1} , whilst values were 50% lower in old sedentary individuals compared with young individuals. In contrast, the $\dot{V}_{\text{O}_2\text{max}}$ in active old individuals was as high as in the young cohort. Cholesterol, which tends to increase with age (the value in the young group being 3.8 mM and in the old sedentary group, 5.3 mM) tended to be lower in old active (4.9 mM). Plasma triglyceride levels were 0.8 mM in the young group, 1.5 mM in the old sedentary group, but 1.0 mM in the old active group. Thus, individuals who perform exercise for long periods in their lives have a more 'healthy' phenotype than those who do not exercise. As illustrated in Fig. 1, this healthy phenotype will lower the risk of secondary ageing and premature death.

To sum up, older persons lose both their capacity to respond to exercise and their capacity to adapt to it (Vina *et al.* 2013b). In our opinion, adapting to exercise

is more relevant in terms of health than responding to it. It is very important to point out that if an active lifestyle is maintained over long periods during one's life, one maintains a healthier, 'younger' phenotype. The experiments we have just reported indicate that exercise can be considered as an intervention to improve life and healthy ageing (see below) (Vina *et al.* 2012) and therefore, since we are dealing with the long-term practice of exercise, one can say that it can be considered as a physiological supplement to improve life and healthy ageing (see below).

Special precautions needed in the prescription of exercise at old age

Older individuals are living with a significant burden of chronic disease, impairments in vision, cognition and hearing, and reduced physiological reserve (Vina *et al.* 2013b). They have an increased susceptibility to age-related diseases, such as cancer, cardiovascular and neurodegenerative diseases, and insulin-independent diabetes. In diabetic patients (both types I and II) exercise should be postponed if blood glucose is >2.5 g L^{-1} together with ketonuria and >3.0 g L^{-1} even without ketonuria, in both cases before it is corrected (Caspersen *et al.* 2012) (see Fig. 2).

Although the heart significantly benefits from physical activity, the incidence of heart failure increases with age, largely due to the development of heart failure risk factors such as hypertension and coronary artery disease. Thus, exercise should be prescribed with caution to these individuals (Vigen *et al.* 2012; Vina *et al.* 2012). Dyspnoea at rest, aortic stenosis, pericarditis, myocarditis, endocarditis, fever and severe hypertension are all contraindications of exercise (Pedersen & Saltin, 2006). In patients with hypertension and active proliferative retinopathy, high-intensity training or training involving Valsalva-like manoeuvres should be avoided. Patients with neuropathy and incipient foot ulcers should refrain from activities entailing the bearing of the patient's own body weight. Age-related endothelial dysfunction and increased arterial stiffness contribute to the increased prevalence of hypertension, particularly systolic hypertension, among the elderly (Pimenta & Oparil, 2012). Hypertensive patients with a blood pressure higher than 180/105 should begin pharmacotherapy before regular physical activity is initiated (Pescatello *et al.* 2004) (see Fig. 2).

The beneficial effects of exercise to the lungs are also well established. There are no absolute contraindications to very moderate exercise in chronic obstructive pulmonary disease patients (Pedersen & Saltin, 2006). However, acute exacerbations of the disease are associated with increased mortality and hospitalization, especially in older individuals (Abbatecola *et al.* 2011). As in asthma

patients, a pause in training is recommended when an acute exacerbation occurs. In cases of infection, a pause in training is recommended until the patient has been asymptomatic for a day, whereafter training can be slowly resumed (Pedersen & Saltin, 2006) (see Fig. 2).

There are conditions, such as osteoarthritis and rheumatoid arthritis, in which exercise is contraindicated and leads to acute phases of the disease. Exercise is also contraindicated in cases of acute joint inflammation if pain worsens after training (Pedersen & Saltin, 2006).

With increasing age, there is a significant reduction in bone formation. Age-related bone loss is also seen in men (Demontiero *et al.* 2012). The training of patients with osteoporosis should include activities with a low risk of falling (Pedersen & Saltin, 2006).

Cancer in older persons is an increasingly common problem, due to the progressive prolongation of the life-expectancy of the Western population (Carreca *et al.* 2005). Exercise is contraindicated in cancer patients being treated with chemotherapy or radiotherapy when a leukocyte concentration falls below $0.5 \times 10^9/L$, haemoglobin below 10 g dL^{-1} , thrombocyte concentration below $20 \times 10^9/L$, and temperature above 38°C . Patients with bone metastases should not perform strength conditioning at high load (Pedersen & Saltin, 2006).

Cell signalling pathways in exercise and ageing

Exercise causes vast changes in many physiological and metabolic parameters in the organism to meet the increase in energy demands associated with it. The most obvious is the increase in oxygen consumption that increases from approximately 200 ml min^{-1} in a person of 70 kg in weight to more than 10-fold in an untrained adult (Hawley *et al.* 2014). This obviously requires significant changes in cell metabolism. Important changes in cell metabolites during exercise include the ATP/ADP ratio, lower creatine phosphate, an increase in fatty acid oxidation, an increase in reactive oxygen species, a decrease in the pH and changes in calcium (Hood, 2001; Gomez-Cabrera *et al.* 2015) (see Fig. 3). These changes led us to consider the major enzymes that contribute to alterations and adaptations in energy metabolism in the cell. AMP-activated protein kinase (AMPK) is an obvious candidate as it is activated by increasing levels of AMP, but this is not the only enzyme that responds to exercise (Canto *et al.* 2009). Calcineurin and calmodulin-dependent kinases are also involved and we observed that mitogen activated protein kinases (MAPKs) like ERK1/2 and p38 are also important (Gomez-Cabrera *et al.* 2005). Finally, the mammalian target of rapamycin (mTOR) is involved in the final steps in the adaptation of muscles to increasing demands of

EXERCISE IS CONTRAINDICATED			
DIABETES	CARDIOVASCULAR DISEASE	INFLAMMATORY DISEASE	CANCER
In patients with blood glucose levels: <ul style="list-style-type: none"> • $>2.5 \text{ g/L}$ together with ketonuria • $>3.0 \text{ g/L}$ even without ketonuria 	In patients with: <ul style="list-style-type: none"> • Dyspnoea at rest • Aortic stenosis • Fever • Severe hypertension ($>180/105$) • Pericarditis • Endocarditis • Myocarditis 	In patients with: <ul style="list-style-type: none"> • Osteoarthritis • Rheumatoid arthritis • Acute joint inflammation (if pain worsens after training) 	In patients with chemotherapy or radiotherapy treatment when: <ul style="list-style-type: none"> • Leukocyte: $<0.5 \times 10^9/L$ • Hemoglobin: $<10 \text{ g/dL}$ • Thrombocyte: $<20 \times 10^9/L$ • Temperature: $>38^\circ\text{C}$
TYPE OF EXERCISE TO AVOID			
HYPERTENSION; ACTIVE PROLIFERATIVE RETINOPATHY	NEUROPATHY; INCIPIENT FOOT ULCERS	BONE METASTASIS	
Patients should avoid: <ul style="list-style-type: none"> • High-intensity Valsalva-like manoeuvres 	Patients should avoid: <ul style="list-style-type: none"> • Activities entailing the bearing of their own body weight 	Patients should avoid: <ul style="list-style-type: none"> • Strength conditioning at high load 	
TYPE OF EXERCISE RECOMMENDED			
OSTEOPOROSIS	CHRONIC OBSTRUCTIVE PULMONARY DISEASE		
Patients should perform: <ul style="list-style-type: none"> • Activities with a low risk of falling 	Patients should perform: <ul style="list-style-type: none"> • Very moderate exercise • If acute exacerbation occurs, a pause in training • In cases of infection, a pause in training until asymptomatic for a day and resume training slowly 		

Figure 2. Special precautions needed in the prescription of exercise at old age

Exercise is absolutely contraindicated in some conditions of the age-related diseases while, in another cases, a particular type of exercise should be avoided or, conversely, is recommended.

energy, especially to increase muscle protein synthesis associated with strength training (Drummond *et al.* 2009). The insulin-like growth factor (IGF) related pathway is critical to increase protein synthesis after exercise (Coffey & Hawley, 2007). It involves PI3K, AKT and mTOR, leading to an activation of p70S6K (Liu *et al.* 2002). The AMPK signals for a lower energy state in the cell and inhibits mTOR, telling the cell that protein synthesis should not be activated in endurance exercise (Atherton *et al.* 2005). However, MP-activated protein Kinase (AMPK) is essential to increase the rate of peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) synthesis. PGC-1 α (which is also activated by p38 MAP kinase) is an important co-factor to activate the biosynthesis of mitochondria (Puigserver *et al.* 1998; Gomez-Cabrera *et al.* 2008). So we are faced with a two-sided adaptation. When anaerobic (strength) training activates IGF-1, the mTOR pathway is activated and muscle protein synthesis is stimulated through mRNA translation and ribosomal biogenesis. When, however, the energy state of the cell is lowered by aerobic exercise, AMPK is activated, mTOR is inhibited and PGC-1 α becomes active leading to mitochondrial biogenesis (Hawley *et al.* 2014).

However, this is the case in young animals. We have observed that mitochondrial biogenesis in old animals

closely resembles that of PGC-1 α knock-out animals, i.e. its activation by aerobic exercise is very weak (Derbre *et al.* 2011). We studied this phenomenon in some detail and came to the conclusion that p38 (an essential activator of PGC-1 α) is continuously activated in old animals. It has to be said now that p38 is an indicator of oxidative stress and cells from old animals are under constant oxidative stress, as proposed by the free radical theory of ageing (Vasilaki *et al.* 2006; Vina *et al.* 2013a). Thus, p38 activation, which is continuous, ceases to be a signal to activate PGC-1 α and the latter becomes non-reactive to the former. This is a very important difference between the muscles of old and young animals. Figure 3 shows that mitochondrial biogenesis is inhibited in muscle of old animals and that this may be due to the non-sensitivity of PGC-1 α to p38 activation.

Moreover, resistance exercise training studies typically show an attenuated muscle protein anabolic response in older compared with younger adults due to a dysregulation in the mTORC1 signalling pathway (Kosek *et al.* 2006; Slivka *et al.* 2008; Mayhew *et al.* 2009). As mentioned in the previous paragraph, one hypothesis that could explain this impairment is that older adults display an increase in markers of cellular stress that may affect the remodelling response following resistance exercise (Drummond *et al.* 2008).

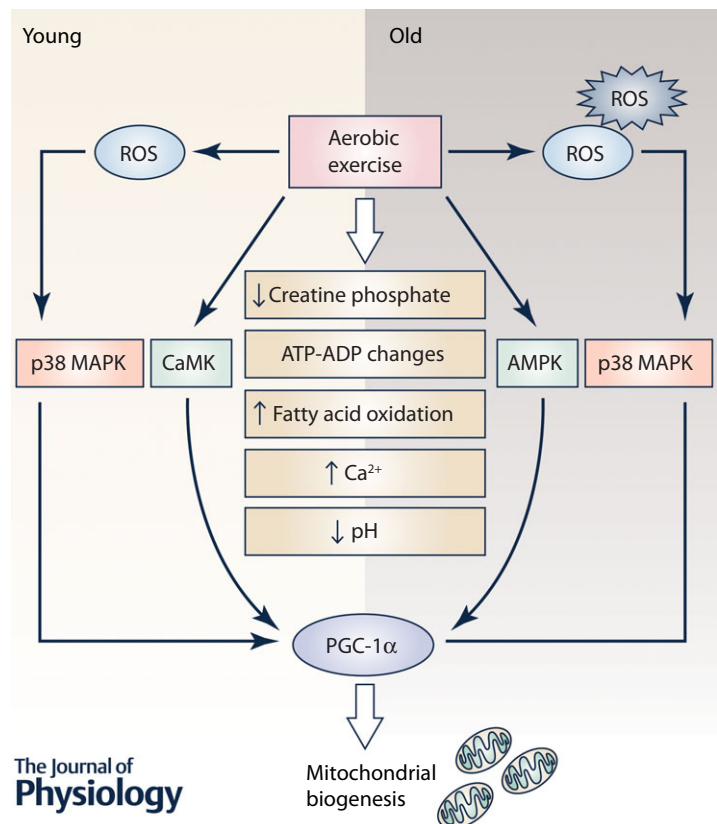


Figure 3. AMP-activated protein kinase (AMPK), calcineurin- and calmodulin-dependent kinases and mitogen activated protein kinases (MAPKs) like p38 are related to changes in cell metabolism during muscle contraction

They are involved in the rate of activation of PGC-1 α , an important co-factor present in mitochondrial biogenesis. In the muscles from old animals these physiological pathways may be disrupted because their cells are under constant oxidative stress that activates p38 continuously, leading to a lack of reactivity of PGC-1 α .

The experiments we have just summarised give support to our modified free radical theory of ageing (Vina *et al.* 2013a). We postulated that free radicals are not directly involved in damage associated with ageing, but rather in the impairment of cell signalling pathways. The altered mitochondrial biogenic pathway in ageing is an example supporting the role of free radicals by altering cellular signalling pathways in ageing.

Concluding remarks: exercise as a supplement for better ageing

We would now like to extend our previous view that exercise is a beneficial physiological stimulus to delay the onset of frailty to viewing exercise as a 'supplement'.

Millions of people worldwide are, and have been, taking supplements for decades, especially nutritional supplements, to improve their health and in the specific area of exercise, to improve their physical condition. Among those who supported supplements were scientists of the stature of Linus Pauling (Pauling, 1986).

Scientific evidence has proved that supplementing with high doses of antioxidants is detrimental for human health (Bjelakovic *et al.* 2004, 2007) and we found that supplementing athletes with vitamin C hampers the efficiency of training (Gomez-Cabrera *et al.* 2008). However, there is no doubt that exercise considered as a lifelong supplement is very good for one's health. Exercise, even if performed at the highest intensity by well-trained people, is hypothesised to enhance longevity. We found that Tour de France cyclists display an average longevity 11% higher than the general population (Sanchis-Gomar *et al.* 2011). As we stated at the beginning of this review, the London bus study proved for the first time that exercise is good for one's health. We would like to propose that exercise should be considered as a 'physiological supplement'. The FDA defines a clear-cut difference between a drug and supplement: a drug is something that has to be proved to be effective in order to be used in clinics; a supplement, on the other hand, is something that can be used unless it is proved to be unhealthy. We would like to propose that exercise should be considered as a physiological supplement for the general population to improve health. Ample scientific evidence supports treating exercise as a supplement with guidance for specific regimes of exercise to promote healthy ageing.

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Additional information

Competing interests

None declared.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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