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SI: FRAILTY, AGEING AND INFLAMMATION

Moving against frailty: does physical activity matter?

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Abstract Frailty is a common condition in older persons and has been described as a geriatric syndrome resulting from age-related cumulative declines across multiple physiologic systems, with impaired homeostatic reserve and a reduced capacity of the organism to resist stress. Therefore, frailty is considered as a state of high vulnerability for adverse health outcomes, such as disability, falls, hospitalization, institutionalization, and mortality. Regular physical activity has been shown to protect against diverse components of the frailty syndrome in men and women of all ages and frailty is not a contra-indication to physical activity, rather it may be one of the most important reasons to prescribe physical exercise. It has been recognized that physical activity can have an impact on different components of the frailty syndrome. This review will address the role of physical activity on the most relevant components of frailty syndrome, with specific reference to: (i) sarcopenia, as a condition which frequently overlaps with frailty; (ii) functional impairment, considering the role of physical inactivity as one of the strongest predictors of physical disability in elders; (iii) cognitive performance, including evidence on how exercise and physical activity decrease the risk of early cognitive decline and poor cognition in late life; and (iv) depression by reviewing the effect of exercise on improving mood and increasing positive well-being.

Keywords Physical activity · Frailty · Elderly

It is exercise alone that supports the spirits, and keeps the mind in vigor.

Marcus Tullius Cicero.

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The life expectancy of older people continues to increase, with persons aged 70 years and more representing the fastest growing segment of the western population (Manton and Vaupel 1995). While prolongation of life is a significant public health aim, at the same time the extended life should involve preservation of the capacity to live independently and to function well. Consequently, the identification of cost-effectiveness interventions to prevent frailty is one of the most important challenges of public health.

Frailty is a geriatric syndrome resulting from age-related cumulative declines across multiple physiologic systems, impaired homeostatic reserve and a reduced capacity of the organism to resist stress, thus increasing vulnerability towards adverse health outcomes including falls, hospitalization, institutionalization and mortality (Bauer and Sieber 2008; Fried et al. 2001). Fried et al. (2001) developed a phenotypic description of physical frailty based on specific physical aspects; three or more of the following characteristics support a frailty diagnosis: unintended weight loss, exhaustion, weakness, slow gait speed, and low physical activity. Other definitions of frailty include components related to cognitive impairment, urinary incontinence, presence of multiple comorbidities (Rockwood et al. 2005; Rolfson et al. 2006).

Furthermore, normal cognitive performance, mood, mobility and independence in activities of daily living represent tasks that are necessary for the maintenance of independent living. Indeed, many authors consider cognitive function and depressed mood in frailty syndrome because they are associated with a serious decline in functional health and confer an increased risk of institutionalization and death (Rothman et al. 2008; Avila-Funes et al. 2009).

Regular physical activity has been shown to protect against diverse components of the frailty syndrome in men and women of all ages (Peterson et al. 2009). It is important to recall that physical activity is defined as movement that involves muscle contraction and includes activity during the daily life such as, housework, gardening, walking, climbing stairs, while exercise is a specific form of physical activity that is a planned physical activity with the intention of acquiring fitness or other health benefits (Carnethon et al. 2009). The most recent recommendations advise people of all ages to include a minimum of 30 min of physical activity of moderate intensity (such as brisk walking) on most, if not all, days of the week (Carnethon et al. 2009). For most people, greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or longer duration. In older persons, exercise and physical activity have much of the same function as in the young, and frailty is not a contra-indication to physical activity, rather it may be one of the most important reasons to prescribe physical exercise. The literature on exercise training in the frail elderly between the ages of 80 and 100 years in nursing homes includes no reports of serious cardiovascular incidents, sudden death, myocardial infarction, exacerbation of metabolic control or hypertension (Zak et al. 2009; Peri et al. 2008). In addition, physical activity and exercise are associated with improved neuropsychological function, especially on cognitive impairment and depression (most common forms susceptible to aging) in older persons (Klusmann et al. 2010). It has been suggested that exercise causes an improvement in an age-reduced cardiovascular function which in turn promotes correct cerebral neuronal activity and reduces pro-inflammatory cytokines.

This review will focus on providing evidence for the benefits of both physical activity and exercise on preventing frailty as well as, explore the impact across some specific components of frailty including, sarcopenia, functional impairment, cognitive performance and depression.

Physical activity and sarcopenia

One of the most serious consequence of human aging is the progressive decline in skeletal muscle mass, that may lead to decreased strength and functionality. Sarcopenia (*Greek sarx* or *flesh* + *penia* or *loss*) has been defined as the loss of skeletal muscle mass and strength that occurs with advancing age (Morley et al. 2001).

The major risk factors and related mechanisms potentially influencing the skeletal muscle decline are the ageing process itself, genetic susceptibility, behavioural factors (less-than-optimal diet, bed rest or sedentary lifestyle), changes in living conditions, many different chronic health conditions and certain drug treatments (Sayer et al. 2008). In most of the cases, sarcopenia is associated with poor endurance, physical inactivity, slow gait speed and decreased mobility. Furthermore, it is highly predictive of incident disability, poor quality of life and all-cause mortality (Cruz-Jentoft et al. 2010a, b).

Even though sarcopenia and frailty are both considered highly distinct entities with regard to functionality and independence in the elderly, there is a significant overlapping between them; most frail older people exhibit sarcopenia, and some older people with sarcopenia are also frail (Bauer and Sieber 2008). The general concept of frailty, however, goes beyond physical factors to include psychological and social dimensions as well, including cognitive performance, mood status, social support and other environmental factors (Topinkova 2008). Furthermore, frailty is regarded as a geriatric syndrome of decreased reserve and resistance to stressors across multiple physiologic systems resulting in a decline in organ function and functional reserve. In particular, decreased functional reserve, which encompasses sarcopenia, may have a crucial role in the development of the frailty syndrome. In this respect, identifying subjects with sarcopenia seems to be an important task both for clinical practice and for selection of individuals for specific treatments in order to prevent frailty.

The consequences of sarcopenia in older people are serious and all health care professionals are challenged to identify the natural course of sarcopenia, and to develop effective treatment strategies (Landi et al. 2010). A sedentary lifestyle has been shown to be a risk factor for muscle weakness that, in turn, results in reduced activity levels, loss of muscle mass and muscle strength. A recent consensus report has hypothesized that specific programs of physical activity represent the most important approach to slow down the decline of muscle mass and muscle strength associated with aging in order to specifically treat sarcopenia (Cruz-Jentoft et al. 2010a, b).

However, the amount of protection is related to the type and intensity of physical activity and exercise. The precise type and duration of endurance or resistance training necessary to completely abolish sarcopenia is still under investigation worldwide. Indeed, resistance training has been demonstrated to be associated with glycolytic metabolism and low mitochondria density; on the other hand, endurance training results in oxidative metabolism and high mitochondrial density (Rolland and Pillard 2009). Recommendations for adult and older people include a balance program of both endurance and strength exercises, performed on a regular schedule (at least 3 days per week). However, it is important to address that specific modification of these recommendations is sometimes necessary for preventing frailty in older persons (Table 1). There are numerous clinical trials that have investigated the specific recommendations, benefits and potential risks associated with endurance and resistance training in older persons (Table 1).

Finally, it is important to underline that the response of muscle cells to specific and different exercises is also under the control of specific genes and nutritional factors (Rolland and Pillard 2009). Thus, genetic background and nutrition should not be overlooked when analyzing the impact of physical activity on frailty.

Physical activity and functional impairment

Physical inactivity is one of the strongest predictors of physical disability in elders (Kortebein et al. 2007). Longitudinal studies have demonstrated that regular physical activity extends longevity and also reduces the risk of physical disability (Leveille et al. 1999; LaCroix et al. 1993). Physical activity started in late life continues to improve the functional autonomy and to reduce mortality, having a strong effect even when controlling for potential adverse risk factors such as smoking, hypertension, family history of hereditary diseases (i.e., cardiovascular diseases, cancer, diabetes), and obesity (Blair et al. 1995). However, the relative contribution of low to moderate intensity of regular physical activities to reduce disability is still unclear. Indeed some authors have demonstrated that only participation in vigorous physical activity and/or high intensity exercise program is associated with reductions in functional decline (King et al. 1993; Cress et al. 1999), whereas others have extended these benefits to low to moderate activities (LaCroix et al. 1993; Landi et al. 2008).

Analysis of more than 10,000 older adults participating in the Established Populations for Epidemiologic Studies of the Elderly (EPESE studies) showed an almost two-fold increased likelihood of dying without disability among those most physically active compared to those who were sedentary (Leveille et al. 1999). Similarly, other studies demonstrated that moderate to vigorous leisure-time physical activity

Table 1 Data from clinical trials on the benefits and potential risks of different types of exercise aimed at preventing frailty in older persons

	Endurance training (also called cardiovascular or aerobic training)	Resistance training (also called strength training or weight lifting)
General principles (Elsawy and Higgins 2010)	Use of large muscle groups Many repetitions At low resistance	Contraction of various muscle groups Few times against a moderate or high resistance
Specific recommendations (Carnethon et al. 2009)	Choose a low impact of aerobic exercise. Examples include: walking, cycling, dancing Start with low intensity (40% of maximum heart rate) and short duration (5 min) Always warm-up and cool-down	Measure baseline strength and use a load at least 40-50% of this as the initial training stimulus Choose a few major paired (agonist–antagonist) muscle groups (i.e., hip and knee extensors, elbow flexors and extensors) Train both sides for full range of motion Add weights in small increments
Benefits (King et al. 2000; Cress et al. 1999; Ettinger et al. 1997; Messier et al. 2000; Miszko et al. 2003; Gauchard et al. 2003)	Improved cardiovascular efficiency Improved body composition (increased ratio of lean to fat mass) Metabolic changes (improved insulin sensitivity and lipid profile) Increased muscular endurance (increased oxygen extraction, capillary density, glycogen storage) Adjunctive treatment of chronic diseases (obesity, arthritis, cardiovascular disease, peripheral vascular disease, diabetes, hypertension, osteoporosis)	Increased force, work, and power capabilities, which may translate into improved functional independence, gait and balance Increased lean body mass Increased range of motion (flexibility) Improved strength of trained muscle group (stabilization, decreased pain from degenerative joint disease, and reduced likelihood of injury)
Potential risks (McCartney 1999)	Cardiac event (MI, sudden death) Musculoskeletal injury (particularly knee and ankle)	Musculoskeletal strain, fractures of osteoporotic bone Exacerbation of underlying joint disease

decreased the risk of poor physical functioning and had the capacity to postpone the onset of disability (Blair et al. 1995; King et al. 2000; Cress et al. 1999; Landi et al. 2008). Recently, using the information collected with the MDS-HC—a comprehensive and standardized geriatric assessment instrument (Bernabei et al. 2008), the AdHOC study showed that a moderate physical activity has an important prognostic influence for geriatric patients living in the community, independently from age and other clinical and functional variables (Landi et al. 2007, b). Even adjusting for several confounders, such as comorbidity and cognitive impairment, incident disability was more frequently reported in the lowest level of physical activity group (less than 2 h) (Landi et al. 2007, b). Similarly, in a cohort of older Finnish men and women, those involved in a high level of everyday physical activity (household chores, walking and gardening) showed significantly less decline in knee extension strength and grip strength after 5 years, as compared to those who were sedentary (Rantanen et al. 1997).

The benefits of physical activity to prevent disability and/or functional performance derive not only from observational studies. Several randomized clinical trials have demonstrated the positive effects of specific physical activity programs in diseased or frail older adults (Ettinger et al. 1997; Chin et al. 2008; Daniels et al. 2008; Binder et al. 2005; Messier et al. 2000). For example, in FAST study (Ettinger et al. 1997), a randomized trial conducted among 439 community dwelling older adults with knee osteoarthritis, self-reported physical function was significantly improved among those participating in an 18-months aerobic exercise training or resistance exercise training program, as opposed to those participating in a health education program. The FAST exercise programs also significantly improved objective physical performance, walking speed and postural balance (Messier et al. 2000). Furthermore, progressive resistance training in a large group of older persons with frailty induced improvements in maximal voluntary thigh muscle strength and whole body FFM after 3 months of training (Binder et al. 2005).

The benefit of exercise on physical function may be mediated by a direct positive effect on impairments, such as reduced muscle strength (36 and impaired balance) (Gauchard et al. 2003).

In healthy older adults, the beneficial physiological effects of specific physical activity program on preventing frailty have also been demonstrated. Regular exercise increases aerobic capacity, muscle strength and endurance, since it emphasizes aerobic conditioning and/or strength training. Despite these findings, it remains unclear whether the positive effects of physical activity interventions can be sustained for a adequate duration of time and maintained at sufficient intensity to prevent incident disabilities.

Down-regulated inflammation is another supposed mechanism by which physical activity may play and important role against physical impairment and disability. Some authors have hypothesized that the participation in regular physical activity programs lowers C-reactive protein (CRP) and interleukin-6 (IL-6). Observational data in young and elderly persons show that greater physical activity is associated with lower CRP and IL-6 levels (Geffken et al. 2001). Recently, in a single-blind, randomized, controlled trial—the Lifestyle Interventions and Independence for Elders (LIFE) trial—Nicklas et al. (2008) demonstrated that greater physical activity results in lower systemic concentrations of IL-6 in elderly individuals, and this benefit is most pronounced in individuals at the greatest risk for disability and subsequent loss of independence. In addition, several small or uncontrolled studies have shown an effect of aerobic exercise training on reducing CRP and IL-6 in middle-aged and/or older persons (Brinkley et al. 2009; Lakka et al. 2005).

Although the findings of these studies indicate that increasing physical activity can be advocated as an effective therapy for reducing inflammation biomarkers, whether this reduction resulted in a positive impact on risk factors for adverse health conditions associated with inflammation was not tested.

Physical activity and cognitive performance

Although the prevention of cognitive impairment has become one of the most important public health priorities, there is still a lack of information about potential preventive strategies. Every effort to identify potential protective factors is required for formulating effective interventions for preventing cognitive decline and dementia. Increasing evidence from experimental and human studies suggest that exercise and physical activity decreases the risk of early cognitive decline and poor cognition in late life (Verghese et al. 2003; Weuve et al. 2004). Recent data from the Nurses' Health Study (Weuve et al. 2004) and the Honolulu Heart Program Study (Abbott et al. 2004) support the hypothesis that regular physical activity, including walking, may prevent decline in cognitive function in both women and men. On the other hand, data from the Bronx Aging Study (Verghese et al. 2003) suggest that the association between physical activity and dementia is weak, while providing evidence for the important and protective effect of cognitive activities—such as leisure activities—on the risk of dementia. While the protective effect of cognitive activities is supported (Wilson et al. 2002), the possible overlap with physical activity may make it difficult to understand the relationship between active lifestyles and dementia. A large observational study among independent older subjects showed that low levels of walking time were predictive of higher rates of dementia (Podewils et al. 2005); furthermore, a randomized control study demonstrated selective improvement in executive control processes after 6 months of aerobic physical activity (Kramer et al. 1999). A recent trial showed that in healthy older women, an exercise program and computer classes were associated with beneficial effects on cognitive performance (Klusmann et al. 2010).

Findings of prospective studies of physical activity and the risk of cognitive impairment are inconsistent, especially considering the characteristics of the studied population, the types of physical activity, and the length of follow-up. Another important issue is that most of these studies were able to assess physical activity levels only during older adult life; however, it is unclear during what period of life physical activity is most relevant to preserving cognitive performance. In a large study of community-dwelling older adults, an inverse association between physical activity and cognitive impairment has been observed (Landi et al. 2007, b). In this study the high intensity physical activity is associated with lower impaired cognitive performance, irrespective of potential confounders. Although this is a retrospective study, the potential benefit of physical activities performed during young and adult ages on cognitive functioning in late life has been considered. In fact, lifetime physical activity always preceded the development of cognitive decline in old age, permitting causal interpretation of these results by time sequence (Landi et al. 2007, b).

The relationship between physical activity and cognitive performance may be modulated by many factors, including environmental and lifestyle exposure which may affect cognitive capacity. For example, subjects with a history of high intensity physical activity during young and adult ages may be more involved in social activities. Otherwise, physical activity may be an indicator of a healthier lifestyle, resulting in less exposure to factors that affect cognitive function. However, some studies showed that the correlation between physical activity and cognitive performance is independent from other socio-economic factors, adjusting the analyses for educational level and other possible potential confounders, such as smoking habits and alcohol abuse (Landi et al. 2007, b).

Physical activity plays an important role in lowering cardiovascular risk, reducing blood pressure, increasing high density lipoprotein cholesterol levels, increasing glucose tolerance and, lastly, ensuring adequate cerebral perfusion (Pate et al. 1995). Some authors have also hypothesized that physical activity has a direct effect on brain plasticity and on structural and functioning brain reserves, protecting neuronal structure, increasing the expression of genes involved in the production of neurotrophic factors, and promoting the development of neuronal fibers, synapses and capillaries (Cotman and Berchtold 2002). Physical activity may also influence non-neuronal vascular adaptations, sustaining the brain's vascular health. Experimental studies have demonstrated that physical activity increases cerebral blood flow, enhances cerebral capillary density, and reduces radical oxidative protein deposits (Ide and Secher 2000). In animal models, exercise increases levels of brain-derived neurotrophic factor and other growth factors, stimulates neurogenesis, increases resistance to brain insult and promotes gene expression that may benefit brain plasticity processes (Molteni et al. 2002).

Physical activity and depression

Depression has a huge impact on individuals and society. With a lifetime prevalence of over 15%, depression will be the second leading illness in the world by 2020 as projected by the World Health Organization. Depression afflicts people of all ages, but it can be particularly devastating for older people, who are less likely to seek treatment. The problems include the failure to recognize the symptoms of depression in the elderly and the belief that nothing can be done for people with many reasons to be depressed. Furthermore, depression tends to last longer in elderly adults, in later life it frequently coexists with other medical illnesses and disabilities, and it also increases the risk of frailty (Russo et al. 2007).

Exercise improves mood and increases positive well-being in the short term, especially among those who are already depressed (Bartholomew et al. 2005). It important to address that randomized clinical trials of up to 1 year have shown improvements in symptoms of anxiety and depression among older persons involved in both high- and low-intensity physical activity programs (King et al. 1993). On the other hand, an observational study in older persons failed to show a protective effect of vigorous exercise in patients experiencing depression for more than 5 years (Kritz-Silverstein et al. 2001) and long-term effects of exercise on depressive symptoms and anxiety remain to be demonstrated in clinical trials. Another study showed that an exercise training for patients with Alzheimer disease combined with teaching caregivers how to manage behavioral problems may help decrease the frailty and behavioral impairment that are often prevalent in patients with Alzheimer disease (Teri et al. 2003). In particular these authors found that in patients with higher depression scores at baseline, those in the intervention group improved significantly more at 3 months on depression scores and maintained such improvement even at 24 months (Teri et al. 2003).

The anti-inflammatory properties of physical activity may help to explain the positive impact of such intervention on depressed mood. Indeed, depression has notable immunological hallmarks. Over the last 10 years evidence emerged that depression is associated with activation of the innate inflammatory immune response including alterations in the ability of immune cells to express pro-inflammatory cytokines (Kritz-Silverstein et al. 2001). On the bases of these data, it has been recently formulated the hypothesis that these cytokine abnormalities may have reciprocal influences on the central nervous system and contribute, at least in part, to the pathophysiology of mood disorders (Raison et al. 2006). Evidence showing that physical exercise can improve chronic inflammation, including adaptive responses in inflammatory and redox-sensitive pathways in skeletal muscle, as well as adaptive responses in innate immune cells, both leading to reduced systemic concentrations of pro-inflammatory biomarkers (Nicklas et al. 2008), also suggests a putative mechanism for antidepressant and anxiolytic effect of physical exercise.

It is important to underline that many authors consider both depression and cognitive impairment new components of the frailty syndrome. Up to date, the literature has indicated a positive impact of physical exercise on cognitive impairment and depressive symptoms in older adults. However, these trials have been performed in older adults with disease, but not with frailty. Indeed, there is a great need for intervention trials testing the impact of physical exercise programs on cognitive impairment and depression in older persons with frailty.

Conclusion

Many results suggest that moderate physical activity carried out as part of everyday activities can be of substantial benefit even to frail and older persons. Vigorous exercise is not always required, while regular leisure activities—such as walking, gardening, or housekeeping—seem to be enough to reach considerable benefits.

Older people are repeatedly told about the benefits of physical exercise (Pahor et al. 2006). Encouragement of older men and women to maintain or increase their walking activity can help lose weight, lower blood pressure, improve cholesterol levels, lower blood sugar and slow down osteoporosis. All these positive effects help maintain mobility, prolong independence, and reduce the risk of all-cause mortality. In this respect, health educational authorities and health care organizations together with primary care physicians should encourage all the older people to be physically active even during the extreme ages of life.

Persistent low-grade inflammation is a significant contributor to the patho-physiology of frailty components, including aging-related sarcopenia and disability. Promising data, including those from randomized controlled trials, show that increasing physical activity could be effective for reducing chronic inflammation in old people. This is likely the most important mechanism by which physical exercise can act against frailty. However, the mechanisms by which increased physical activity may reduce persistent inflammation have not been fully explained. If regular exercise emerges as an effective treatment for reducing inflammation, the magnitude of the effect and the amount of exercise necessary to produce clinically meaningful reductions should also be delineated.

Regular exercise is the only therapy found to consistently improve sarcopenia, physical function, cognitive performance and mood in both frail and non-frail older adults. The findings reported that regular exercise was associated with a beneficial impact on improving such specific components related to frailty as well as, prevent their development in older healthy persons. However, some questions remain unresolved. What exercises are best suited and most effective for older people? How can older people be enabled to take more habitual physical activity? For people who have marked physical limitations, are there alternatives to traditional exercise programs? How can nutrition and exercise regimens be combined for prevention of treatment of frailty? Therefore, future research, especially longitudinal randomized controlled trials, will be needed to answer these questions regarding the role of physical activity and exercise on the frailty syndrome in older persons.

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