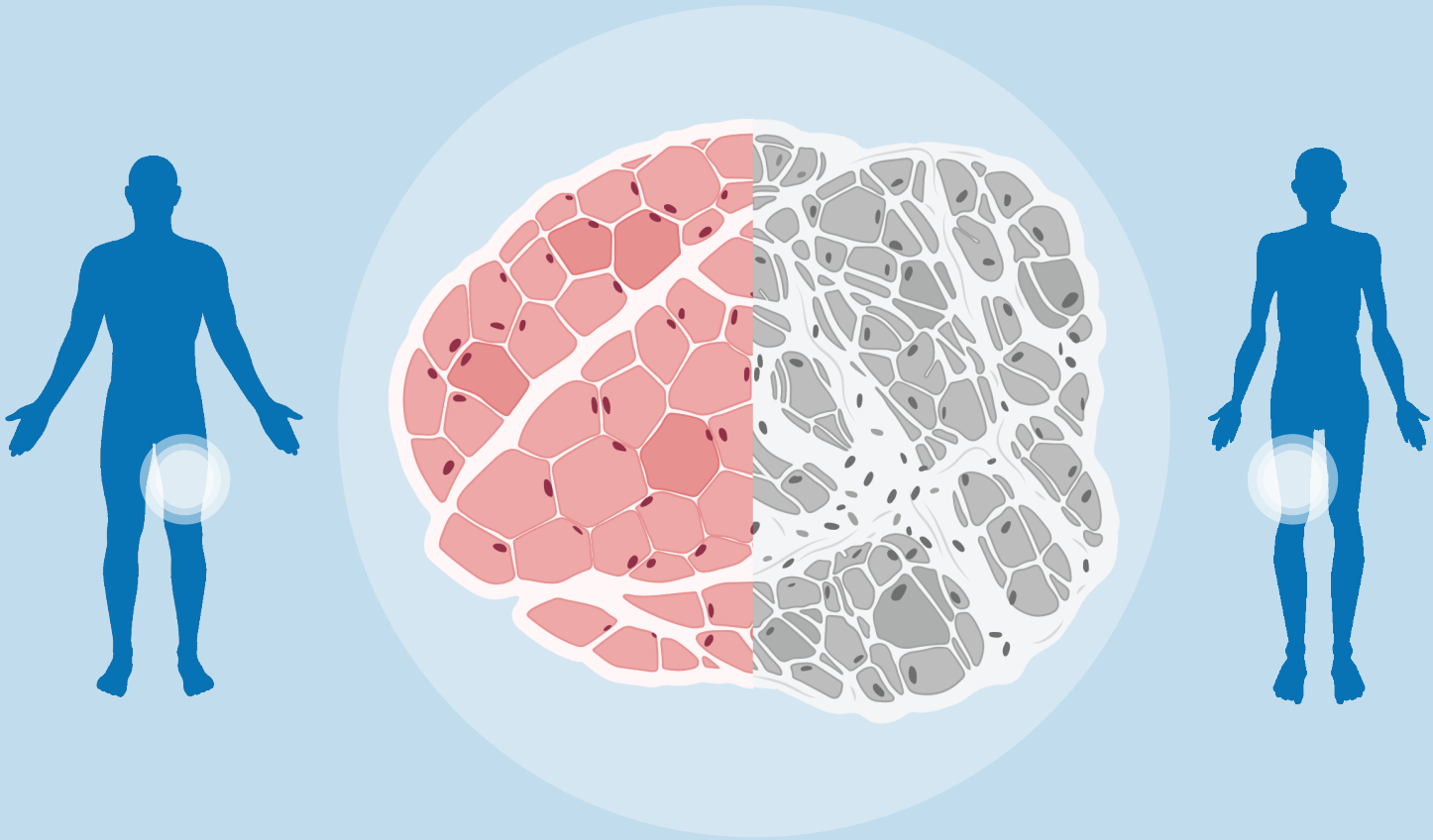
Universidad de Alcalá
Department of Systems Biology

AGING- AND MUSCLE DISUSE-INDUCED FUNCTIONAL DECLINE: PHYSIOLOGICAL MECHANISMS AND PREVENTIVE STRATEGIES

Author **Pedro L. Valenzuela Tallón** | Supervisor **Dr. Pedro de la Villa Polo**



DOCTORAL PROGRAM IN HEALTH SCIENCES
2020

Universidad de Alcalá

Aging- and muscle disuse-induced functional decline: physiological mechanisms and preventive strategies

Pedro L. Valenzuela Tallón

PhD Thesis

Doctoral program in Health Sciences

Supervisor: Prof. Pedro de la Villa Polo

Department of Systems Biology
University of Alcalá
2020

Acknowledgements (agradecimientos)

Agradecimientos personales

Nombrar a todas las personas que han contribuido al desarrollo de mi tesis doctoral y, en definitiva, a mi desarrollo personal y profesional en los últimos años se me hace una tarea imposible; son innumerables y estoy profundamente agradecido a todas ellas. Por ello, querría comenzar pidiendo disculpas por no poder mencionarlas a todas. No obstante, durante estos años he coincidido con muchos compañeros que se han convertido en mucho más que eso, en amigos, y me gustaría darles las gracias.

Gracias a aquellos que presenciaron mis primeros pasos en el laboratorio y me ayudaron a defenderme en un mundo tan desconocido en aquel momento para mí como era la investigación básica con ratones, músculos y células – con la paciencia que eso requería –, y que en los siguientes años me han ayudado a desconectar despegándome de la pantalla para tomar un café (o los que hiciese falta): Laura, Fran, Javi, Andresa, Santi y Mateo.

Gracias a Zigor, Guille, Elaia y Javi por compartir conmigo la enorme afición por el deporte de alto rendimiento y en general las ciencias del ejercicio, por obligarme a buscar siempre el equilibrio entre la teoría y la práctica, y lo más importante, por compartir conmigo innumerables buenos momentos (y pinchos de tortilla en el Picos).

Gracias a Javi y Adri por ayudarme a estar en constante actualización y por hacerme mejorar como investigador y divulgador. Quién diría hace 5 años que Fissac me iba a acompañar en todos los años de la tesis (y los que quedan), y sobre todo que podía encontrar alguien igual de friki que yo (o más, que lo de Adri es caso aparte) de la fisiología del ejercicio.

Gracias a Nik, Nic, Bernd, Enea, Andrea y Samara (y resto de compañeros de Schulthess Klinik) por hacerme tan acogedora la estancia en Zurich, de la cual me llevo una gran experiencia no solo profesional sino especialmente personal. Habéis hecho que fuese el mejor sitio en el que podría haber realizado mi estancia.

Quisiera agradecer también, como no, a las dos personas que más han contribuido a mi formación investigadora. A Pedro, por abrirme las puertas al mundo de la investigación y guiarme desde mis años en la carrera (y ya van unos cuantos) formándome y otorgándome una libertad en algunas ocasiones que, aunque en aquellos primeros momentos me abrumaba, sin lugar a dudas me ha ayudado a estar donde estoy. A Alejandro, por acompañarme durante estos últimos años e inculcarme esa asombrosa motivación por buscar siempre la mejor calidad posible. Habéis sido tan partícipes como yo de esta tesis doctoral.

Y por último, pero más importante, gracias a mi familia y a Bea. A mis padres, por haberme educado en los valores del esfuerzo y en el placer de la búsqueda del conocimiento, y por apoyarme en esta dura e incierta carrera que es la investigación. A Bea, por hacer que sea consciente de lo mucho que me queda por aprender y, sobre todo, por acompañarme, motivarme y aguantarme día a día en los buenos y malos momentos.

Gracias.

Agradecimientos institucionales

Quisiera agradecer también a una serie de instituciones que han jugado un papel fundamental en la elaboración de la presente tesis doctoral. Primero, a la Universidad de Alcalá por permitirme desarrollar este proyecto y en general mi labor profesional con un contrato de Formación del Personal Investigador (FPI2016). Gracias a este contrato he podido completar más de 90 trabajos de investigación que han sido publicados en revistas internacionales, estando aquellos más relacionados con la temática de la presente tesis doctoral enumerados en los Apéndices. Quisiera mostrar también mi agradecimiento a la Agencia Española de Protección de la Salud en el Deporte (AEPSAD) por permitirme desarrollar parte de mi labor investigadora en el Centro de Medicina del Deporte (Unidad de Control de Rendimiento), pues me ha servido para complementar el trabajo presentado en esta tesis doctoral con otra de mis principales líneas de investigación: el deporte de alto rendimiento. Gracias a la Fundación Renal Íñigo Álvarez de Toledo y a todos sus trabajadores (encabezados por la Dra. Blanca Miranda) así como al Servicio de Geriatría del Hospital Universitario Gregorio Marañón (encabezados por el Dr. José Antonio Serra-Rexach) por permitirme conocer más de cerca la excelente labor que realizan con los pacientes y por poner en valor el papel del ejercicio en estas poblaciones. Por último, agradecer a Schulthess Klinik (Human Performance Lab) haberme permitido realizar una estancia de investigación en sus instalaciones, la cual no solo me ha servido solo como experiencia profesional sino también personal.

Abstract

Societies are progressively aging, and those aged >80 years represent the most rapidly expanding population segment. However, this process is associated with an increased incidence of the so-called ‘age-related conditions’, including a greater risk of functional decline that is further exacerbated during some situations such as hospitalization or in patients with chronic diseases. How to counteract aging-induced functional decline is therefore a major challenge for modern medicine. Under this context, the present project aimed to explore the physiological mechanisms underlying aging- and disuse-induced functional decline, as well as to analyze the role of physical exercise as a preventive strategy. Through a compendium of narrative reviews, clinical trials and systematic reviews with meta-analysis, the present project shows how lifelong exercise can attenuate the functional decline commonly observed with aging. Moreover, the benefits of inhospital physical exercise – or the application of exercise mimetics such as neuromuscular electrical stimulation when voluntary exercise is not feasible – in older adults at risk of functional decline such as those hospitalized with an acute medical condition or those who suffer from a chronic disease such as end-stage renal disease are also proven. Although further research is needed to determine the optimal exercise dose attending to the individual patients’ characteristic to maximize responsiveness, the present findings highlight the effectiveness of physical exercise in preventing aging-induced functional decline and support its routine implementation in daily life and particularly during disuse situations.

Resumen

La sociedad está envejeciendo progresivamente, y los mayores de 80 años son actualmente el segmento de la población que más rápido crece. Sin embargo, este proceso está asociado a una mayor incidencia de las denominadas 'enfermedades asociadas a la edad', incluyendo un mayor riesgo de deterioro funcional que se ve aún más exacerbado ante situaciones como la hospitalización o en pacientes con patologías crónicas. Contrarrestar el deterioro funcional asociado a la edad es por lo tanto uno de los principales retos para la medicina moderna. Ante este contexto, el presente proyecto trató de explorar los mecanismos fisiológicos subyacentes al deterioro funcional asociado a la edad y al desuso, así como analizar el papel del ejercicio físico como estrategia preventiva. A través de un compendio de revisiones narrativas, ensayos clínicos y revisiones sistemáticas con meta-análisis, el presente proyecto muestra que realizar ejercicio durante toda la vida puede atenuar el deterioro funcional comúnmente observado con la edad. Además, los beneficios del ejercicio físico intra-hospitalario – o de la aplicación de herramientas alternativas como la electroestimulación muscular cuando el ejercicio voluntario no es factible – son también demostrados. Aunque es necesaria una mayor evidencia para determinar la dosis óptima de ejercicio dependiendo de las características individuales de cada paciente para maximizar el ratio de respuesta, estos hallazgos resaltan la eficacia del ejercicio físico para prevenir el deterioro funcional asociado a la edad y apoyan su inclusión rutinaria en el día a día y especialmente durante situaciones de desuso.

Index

1. Introduction

Our aging world and the associated health consequences

Societies are progressively aging. It has been estimated that the proportion of elderly individuals (*i.e.*, those aged > 65 years) worldwide increased approximately from 9% in 1990 to 12% in 2013, and is expected to reach more than 20% (around 2 billion people in total) by 2050.[1,2] This increase is particularly relevant for those aged 80–85 years, which is expected to more than triple between 2015 and 2050.[1,2]

However, an increase in lifespan does not necessarily mean a greater health-span, and indeed the incidence of the so-called 'age-related conditions' has grown in the last decades. One of the major age-related conditions is sarcopenia (defined as an excessive loss of muscle mass and strength with aging), which is present in approximately 21% of those aged 85 years and above.[3] Moreover, frailty, a multidimensional geriatric syndrome that, similarly to sarcopenia, refers to a decline in muscle mass and strength but also in multiple physiological systems (*e.g.*, endocrine, immune),[4] is also a worryingly prevalent condition (affecting >65% of those aged 90 years and above).[5] These conditions have a major relevance as they are associated with an increased morbimortality and an impaired quality of life,[4,6–8] also increasing hospitalizations costs and the financial burden for health systems.[9,10] For this reason, the development of strategies aimed at improving the so-called intrinsic capacity (defined as the composite of physical and mental capacities of an individual) is a priority to promote healthy aging.[11]

The importance of exercise to attenuate aging-related functional decline

The exponential decline of physical function – as exemplified, for instance, through decreases in maximum oxygen consumption ($\dot{V}O_{2max}$, i.e., the maximum integrative ability of the organism to obtain and use oxygen),[12] widely considered the gold standard

measurement of cardiorespiratory fitness[13] – that occurs with aging is a major contributor to loss of functionality.[14] In this regard, although aging has been traditionally associated with an exponential decline in physical function, this association might be confounded by many factors, notably the increasingly inactive lifestyle that often accompanies the aging process in the general population. Indeed, at least 1 of every 4 individuals perform less than the minimum WHO-recommended amount of physical activity, which is further aggravated during aging[15] Maintaining high levels of physical activity through the lifespan might be a necessary condition to attenuate the age- and inactivity-related decline in physiological function.[16,17] Thus, masters athletes (i.e., individuals > 40 years old who still actively participate in sports competitions) have been proposed as a paradigm of healthy aging because most are able to maintain high levels of exercise and show a remarkable physical and physiological function compared to their sedentary peers.[18–20] Analyzing whether master athletes are able to attenuate aging-related functional decline could therefore provide valuable information regarding the role of lifelong exercise for healthy aging.

The importance of exercise in situations associated with an exacerbation of aging-related functional decline

Apart from the unavoidable progressive decline of intrinsic capacity with aging, some situations such as hospitalization periods and chronic diseases can further exacerbate this decline.[21] Older adults' physical activity levels are commonly low, which is further aggravated with these conditions (thus provoking a condition known as 'muscle disuse').[22–24] For instance, it has been reported that hospitalised older adults spend most of the time in bed even if they are able to walk independently,[25] with nearly 75% of them

do not walking at all during hospitalisation.[26] These low physical activity levels can have important detrimental consequences for older adults. For instance, ten days of bed rest have been reported to result in a reduced muscle mass, strength and functional ability in older adults,[27] but even shorter periods seem enough to induce these detrimental effects in these and other health markers (e.g., activation of catabolic pathways and increased proteolysis).[28,29] Indeed, one of the main consequences associated with hospitalization periods is the so-called 'hospital-associated disability' (HAD), defined as the loss of the ability to independently perform one or more basic activities of daily living (ADL, e.g., bathing, dressing, toileting, transferring from a bed or chair, feeding) during hospitalization.[30] This condition affects approximately one third of hospitalized older adults,[31] and is associated with an increased risk of disability, institutionalisation and short- and long-term mortality.[32–34] Moreover, hospitalization-induced disuse situations have been reported to negatively affect glycemic control in older adults,[35–38] as well as to increase the risk of cognitive decline and dementia.[39] Given that physical activity level during hospitalization – as assessed through an objective method such as triaxial accelerometry – has been identified as a predictor of HAD,[22–24] the promotion of inhospital exercise programs might be a potentially effective strategy for the prevention of functional decline in these patients.

Similarly to what occurs during periods of acute hospitalization, there are some chronic diseases that are associated with an exacerbation of the aging-related functional decline. This is the case of patients with end-stage renal disease (ESRD) treated with hemodialysis. The prevalence of ESRD patients treated with hemodialysis is rapidly growing worldwide – especially among older adults –,[40] and it is estimated to increase by 11-18% until 2030.[41] Hemodialysis patients usually present an impaired functional capacity,[42,43] being the latter and important prognostic factor of mortality in this

population.[44–49] Among other mechanisms (notably a pro-inflammatory status, as well as the presence of comorbidities such as diabetes, malnutrition or anemia), it has been observed that the low levels of physical activity performed by hemodialysis patients –particularly during treatment days –[50] might explain, at least partly, their poor functional capacity.[51]

In summary, the low levels of physical activity usually performed by older adults, particularly by acutely hospitalized ones or by those with chronic diseases such as ESRD might be one of the causes of their physical deterioration. For this reason, physical exercise programs could be a potentially effective strategy for the prevention of aging-induced functional decline, particularly in situations of muscle disuse.

2. Hypotheses and Objectives

Hypothesis

We hypothesized that lifelong exercise – as exemplified by masters athletes – would be associated with an attenuated functional decline with aging. Moreover, we hypothesized that supervised inhospital physical exercise programs – or the use of other passive interventions such as NMES if voluntary exercise is not feasible – would be an effective strategy for preventing functional decline in frail populations such as older adults hospitalized with an acute medical condition or affected by a chronic disease such as ESRD.

Objectives

The present project aimed to:

- Examine the physiological mechanisms underlying aging- and disuse-induced functional decline, and the potential benefits of physical exercise for its prevention.

- Assess the effect of lifelong exercise to prevent aging-induced functional decline.

- Examine the effectiveness of different physical strategies – including voluntary exercise and other potential passive alternatives for patients unable to perform voluntary exercise – for preventing disuse-induced functional decline in older adults.

- Assess the effects of an inhospital exercise programs in older adults hospitalized with an acute medical condition, as well determine potential factors modulating individual responsiveness to this program.

- Assess the effects of intradialytic exercise programs – or the application of passive strategies such as neuromuscular electrical stimulation (NMES) – to counteract functional decline in patients with ESRD.

3. Materials and Methods

This Doctoral Thesis is a compendium of 8 papers (including narrative reviews, clinical trials and systematic reviews with meta-analysis) published in international journals indexed in the Journal Citation Report. The methods of the studies are explained in detail in the papers, which are included in the Results section. The references of these papers are:

- **Valenzuela PL**, Castillo-García A, Morales JS, Izquierdo M, Serra-Rexach JA, Santos-Lozano A, Lucia A (2019) Physical exercise in the oldest old. Comprehensive Physiology. 9 (4): 1281-1304. IF (2019): 6.604. Q1 (6/81).

- **Valenzuela PL**, Maffiuletti N, Joyner MJ, Lucia A, Lepers R (2020) Lifelong Endurance Exercise as a Countermeasure Against Age-Related VO_{2max} Decline: Physiological Overview and Insights from Masters Athletes. Sports Medicine. 50 (4): 703-716. IF (2019): 8.551. Q1 (2/85).

- **Valenzuela PL**, Morales JS, Pareja-Galeano H, Izquierdo M, Emanuele E, de la Villa P, Lucia A (2018) Physical strategies to prevent disuse-induced functional decline in the elderly. Ageing Research Reviews. 47:80-88. IF (2018): 10.390. Q1 (2/53).

- **Valenzuela PL**, de Alba A, Pedrero-Chamizo R, Morales JS, Cobo F, Botella A, González-Gross M, Pérez M, Lucia A, Marín-López, MT (2018) Intradialytic Exercise: One Size Doesn't Fit All. Frontiers in Physiology. 9: 844. IF (2018): 3.2. Q2 (25/81).

- **Valenzuela PL**, Morales JS, Ruilope LM, de la Villa P, Santos-Lozano A, Lucia A (2020) Intradialytic neuromuscular electrical stimulation improves functional capacity and muscle strength in people receiving haemodialysis: a systematic review. Journal of Physiotherapy. 66 (2):89-96. IF (2019): 5.440. Q1 (1/139).

- **Valenzuela PL**, Morales JS, Castillo-García A, Mayordomo-Cava J, García-Hermoso A, Izquierdo M, Serra-Rexach JA, Lucia A (2020) Effects of exercise interventions on

the functional status of acutely hospitalised older adults: A systematic review and meta-analysis. Ageing Research Reviews. 61:101076. IF (2019): 10.616. Q1 (1/51).

- Ortiz-Alonso J, Bustamante-Ara N, **Valenzuela PL**, Vidán-Astiz M, Rodríguez-Romo G, Mayordomo-Cava J, Javier-González M, Hidalgo-Gamarra M, López-Tatis M, Valadés-Malagón MI, Santos-Lozano A, Lucia A, Serra-Rexach JA (2020) Effect of a Simple Exercise Program on Hospitalization-Associated Disability in Older Patients: A Randomized Controlled Trial. JAMDA. 21 (4): 531-537. IF (2019): 4.367. Q1 (8/51).

- **Valenzuela PL**, Ortiz-Alonso J, Bustamante-Ara N, Vidán-Astiz M, Rodríguez-Romo G, Mayordomo-Cava J, Javier-González M, Hidalgo-Gamarra M, López-Tatis M, Valadés-Malagón MI, Santos-Lozano A, Lucia A, Serra-Rexach JA (2020) Individual Responsiveness to Physical Exercise Intervention in Acutely Hospitalized Older Adults. Journal of Clinical Medicine. 9 (3). IF (2019): 3.303. Q1 (36/165).

4. Results

Mechanisms underlying aging- and disuse-related deterioration and potential exercise benefits

In order to summarize the evidence on the mechanisms underlying aging- and disuse-related deterioration, as well as the potential role of physical exercise for its prevention, we performed a narrative review published in Comprehensive Physiology (impact factor: 6.246, position: 5/81, category: Physiology]).[52] In this review we show that aging is associated with an increased risk for intrinsic capacity decline, which is largely a result of a multisystem deterioration including changes at the endocrine, neuromuscular, metabolic, and cardiorespiratory level. However, exercise can be effective in reducing this aging-related deterioration, being also beneficial in already frail elders. A representative scheme is shown as Figure 1.

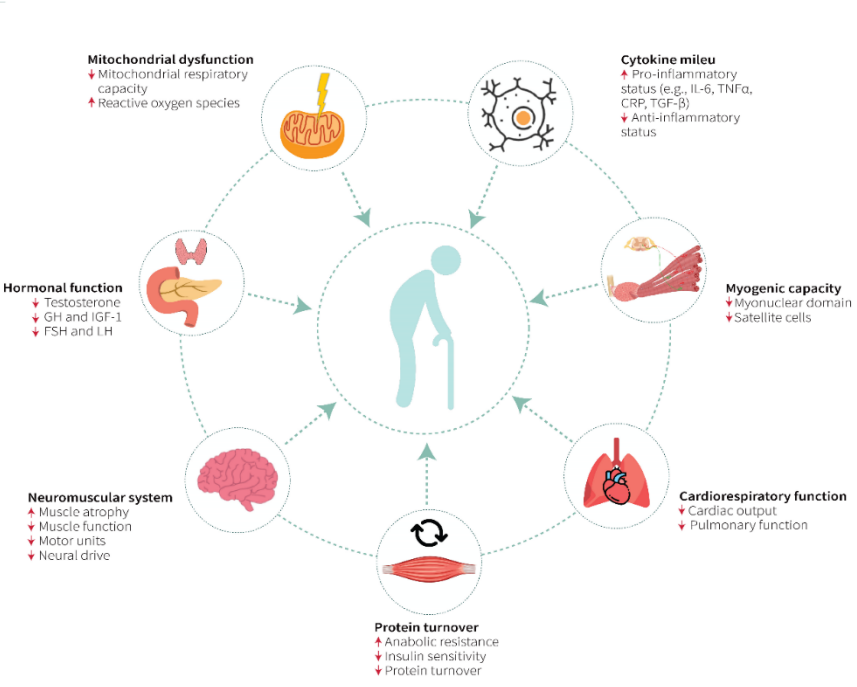


Figure 1. Summary of the multi-systemic physiological mechanisms associated with aging-induced functional decline.

Physical Exercise in the Oldest Old

Pedro L. Valenzuela,[1,2] *Adrián Castillo-García,*[3] *Javier S. Morales,*[4] *Mikel Izquierdo,*[5,6] *José A. Serra-Rexach,*[5,7] *Alejandro Santos-Lozano,*[8] *and Alejandro Lucia*[*4,5]

ABSTRACT

Societies are progressively aging, with the oldest old (i.e., those aged >80–85 years) being the most rapidly expanding population segment. However, advanced aging comes at a price, as it is associated with an increased incidence of the so-called age-related conditions, including a greater risk for loss of functional independence. How to combat sarcopenia, frailty, and overall intrinsic capacity decline in the elderly is a major challenge for modern medicine, and exercise appears to be a potential solution. In this article, we first summarize the physiological mechanisms underlying the age-related deterioration in intrinsic capacity, particularly regarding those phenotypes related to functional decline. The main methods available for the physical assessment of the oldest old are then described, and finally the multisystem benefits that exercise (or "exercise mimetics" in those situations in which volitional exercise is not feasible) can provide to this population segment are reviewed. In summary, lifetime physical exercise can help to attenuate the loss of many of the properties affected by aging, especially when the latter is accompanied by an inactive lifestyle and benefits can also be obtained in frail individuals who start exercising at an advanced age. Multicomponent programs combining mainly aerobic and resistance training should be included in the oldest old, particularly during disuse situations such as hospitalization. However, evidence is still needed to support the effectiveness of passive physical strategies including neuromuscular electrical stimulation or vibration for the prevention of disuse-induced negative adaptations in those oldest old people who are unable to do physical exercise. © 2019 American Physiological Society. *Compr Physiol* 9:1281-1304, 2019.

Didactic Synopsis

Major teaching points

1. Aging is associated with an increased risk for intrinsic capacity decline, which is largely a result of a multisystem deterioration including changes at the endocrine, neuromuscular, metabolic, and cardiorespiratory level.

2. Lifetime physical exercise can help to maintain (or at least attenuate the loss of) many of the properties (notably, muscle mass, functional ability, cardiorespiratory function) affected by aging and especially by inactive aging.

3. Exercise programs are also beneficial in frail elders, including institutionalized or hospitalized individuals.

4. Multicomponent exercise programs (especially if combining aerobic and resistance training) provide multiple systemic benefits, including improvements in neuromuscular, endocrine, cardiovascular, cardiorespiratory, metabolic, and cognitive function.

5. Exercise interventions—or alternatively, passive strategies such as neuromuscular electrical stimulation if volitional exercise is not feasible—should be implemented during disuse situations such as hospitalization.

Introduction

Societies are progressively aging. It has been estimated that the proportion of elderly individuals (i.e., those aged >65 years) worldwide increased approximately from 9% in 1990 to 12% in 2013 and is expected to reach more than 20% (around 2 billion people in total) by 2050 (123, 243). Further,

*Correspondence to alejandro.lucia@universidadeuropea.es

[1]Department of Systems Biology, University of Alcalá, Madrid, Spain

[2]Department of Sport and Health, Spanish Agency for Health Protection in Sport (AEPSAD), Madrid, Spain

[3]Fissac - Physiology, Health and Physical Activity, Madrid, Spain

[4]Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain

[5]Biomedical Research Networking Center on Frailty and Healthy Aging (CIBERFES), Madrid, Spain

[6]Department of Health Sciences, Public University of Navarra, Navarrabiomed, Idisna, Pamplona, Spain

[7]Department of Geriatric, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[8]i+HeALTH, European University Miguel de Cervantes, Valladolid, Spain and Research Institute Hospital 12 de Octubre (i+12'), Madrid, Spain

Published online, October 2019 (*comprehensivephysiology.com*)

DOI:10.1002/cphy.c190002

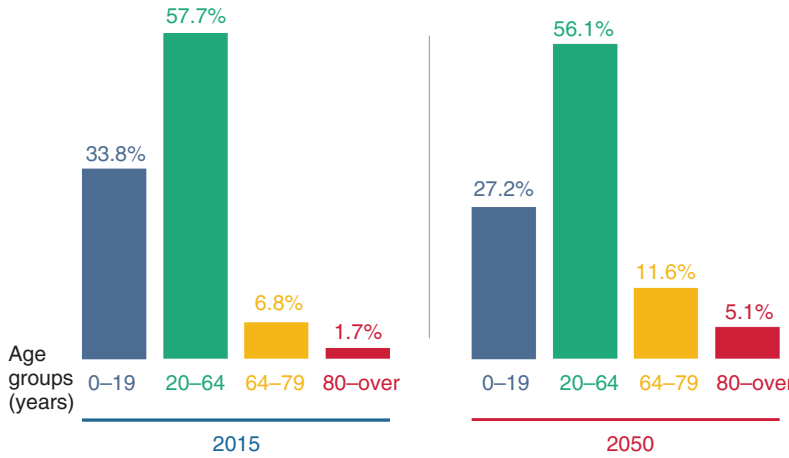


Figure 1 Expected demographic evolution of the different population segments from 2015 to 2050. Data source: U.S. Census Bureau, 2013; International Data Base.

the oldest old, that is, those aged 80 to 85 years and older, are the most rapidly expanding population segment, which is expected to increase more than threefold between 2015 and 2050 (123) (Figure 1). However, an increase in life span does not necessarily mean a greater health span, and indeed, the incidence of the so-called age-related conditions has grown in the last decades. For instance, dementia, the loss of cognitive functioning and behavioral abilities that occurs with aging, affects approximately one quarter of the oldest old, and its incidence is expected to keep growing (173). Sarcopenia, defined as an excessive loss of muscle mass and strength with aging (see below for more details), is also present in about 21% of those aged 85 years and above (82). Moreover, frailty, a multidimensional geriatric syndrome that, similarly to sarcopenia, refers to a decline in muscle mass and strength but also in multiple physiological systems (e.g., endocrine, immune) (41), is also a worryingly prevalent condition (affecting >65% of those aged 90 years and above) (102). In this respect, the development of strategies for improving the so-called intrinsic capacity (defined as the composite of physical and mental capacities of an individual) is a priority to promote healthy aging (19).

This article aims to (i) summarize the physiological mechanisms underlying the age-related deterioration in intrinsic capacity, particularly those related to functional decline; (ii) describe the main methods available for the physical assessment of the oldest old; and (iii) review the multisystem benefits that physical exercise can provide in this population segment in several situations, including hospitalization. Of note, in this article, the term "oldest old" is used to refer specifically to those people aged 80 to 85 years or above (when applicable), whereas the broader term "elderly"/"elder" (or occasionally "older adults") is used for those individuals aged >65 years. Age ranges of study participants are specified when applicable.

Mechanisms Underlying Age-related Deterioration

Several candidate hallmarks have been proposed as the main contributors to the aging process in mammals [for a review, see López-Otín et al. (170)] (Figure 2). Primary hallmarks, which include alterations in nuclear and mitochondrial deoxyribonucleic acid (DNA), telomere loss, epigenetic drift, and defective proteostasis, are all negative processes that progressively hasten aging. In contrast, the effects of antagonistic hallmarks depend on their intensity. This is the case for senescence (i.e., cell degeneration and death), which at low levels protects the organism from diseases such as cancer but that in excess can promote aging, generation of reactive oxygen species (ROS), which mediate cell signaling and survival but can also induce cellular damage, or nutrient-sensing and anabolism, which in excess and maintained chronically can become pathological, notably during cancer. Finally, integrative hallmarks are those that directly affect tissue homeostasis and function, including stem cell exhaustion (i.e., loss of regenerative potential) and altered intercellular communication (e.g., impaired endocrine or neuronal signaling). These "overall" aging hallmarks result in several chronic changes at the multisystem level that eventually promote functional decline and muscle loss (Figure 3).

Cardiorespiratory function

Aging gradually reduces cardiorespiratory function [commonly assessed by measuring an individual's peak oxygen consumption (Vo_{2peak}) reached during incremental exercise involving large muscle mass (treadmill brisk walking/running, cycle-ergometry testing)].

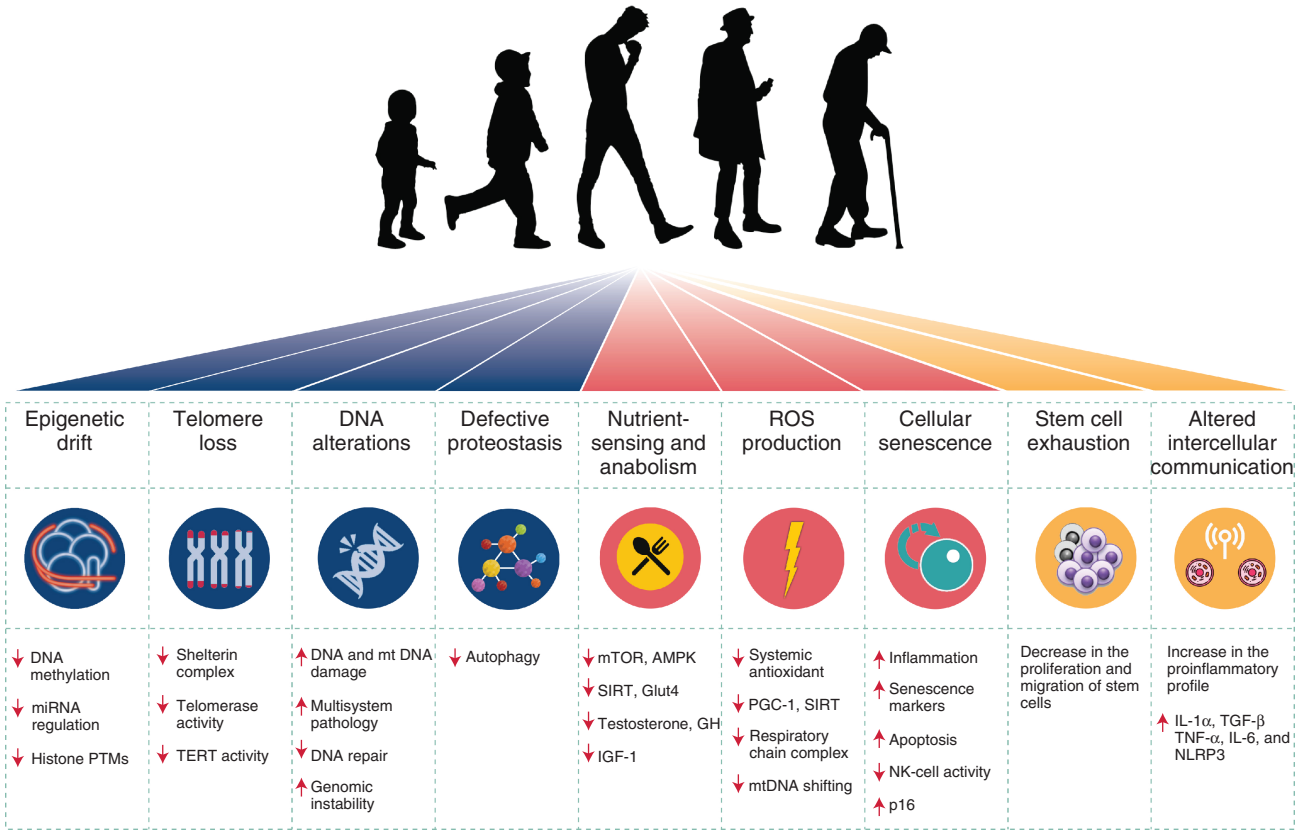


Figure 2 Hallmarks of aging proposed by López-Otín et al. (170). Abbreviations: AMPK, AMP-activated protein kinase; DNA, deoxyribonucleic acid; GH, growth hormone; IGF-1, insulin-like growth factor 1; IL, interleukin; miRNA, micro ribonucleic acid; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; NK, natural killer; NLRP3, NOD-like receptor protein 3; PGC-1, peroxisome proliferator-activated receptor gamma coactivator 1; PTMs, posttranslational modifications; ROS, reactive oxygen species; SIRT, sirtuin; Glut 4; glucose transporter type 4; TERT, human telomerase reverse transcriptase; TNF, tumor necrosis factor.

Changes at the respiratory, cardiovascular, and muscle level can affect Vo_{2peak}. Pulmonary function becomes progressively compromised with aging [for a review, see Aalami et al. (2) and Lowery et al. (172)]. An increase in chest wall stiffness together with a decrease in the strength of respiratory muscles (diaphragm, abdominal muscles) results in a decreased forced expiratory volume (147), and the arterial partial pressure of oxygen decreases progressively due to age-induced ventilation-perfusion mismatch (265). Moreover, the cumulative surface area available for gas exchange (i.e., alveolar surface area) decreases during aging due to alterations in the lung internal geometry (280).

Several changes at the cardiovascular level can also in part explain the age-related decline in Vo_{2peak} [for a review, see Aalami et al. (2) and Lye and Donnellan (174)]. Regarding cardiac structural changes, aging is associated with increases in left ventricular (LV) wall thickness, which is attributed to myocyte hypertrophy (albeit with a progressive loss in their number) together with an accumulation of interstitial connective tissue and amyloid deposits (174). Aging is also associated with increased fibrosis and calcification of the cardiac valves, loss of myocytes in the sinoatrial node, increased stiffness of peripheral and central arteries, and increases in the number of sites for lipid deposition at the vascular level (with subsequent reductions in laminar blood flow) (174). Further, the elderly typically present with a reduced cardiac output (11) and early diastolic filling and higher LV diastolic pressures, together with reduced β-adrenergic responsiveness (with subsequent decreases in maximum heart rate) and reduced capillary density [in both cardiac (174) and skeletal muscle (113)] and coronary reserve (174). Finally, aging is accompanied by an impaired mitochondrial biogenesis and function (55), which may also compromise Vo_{2peak} through decreases in muscles' ability to extract and use oxygen.

Neuromuscular system

Muscle mass decreases at a rate of 1% to 2% per year above the age of 50, and even greater declines are observed in muscle strength, which decreases by approximately 1.5% per year between ages 50% and 60% and 3% thereafter (119). Moreover, skeletal muscle power (i.e., the capacity of the muscle to produce both forceful and rapid contractions) declines more rapidly than muscle strength during aging (231).

Regarding muscle mass loss, changes in muscle protein turnover seem to be the eventual underlying mechanisms (see

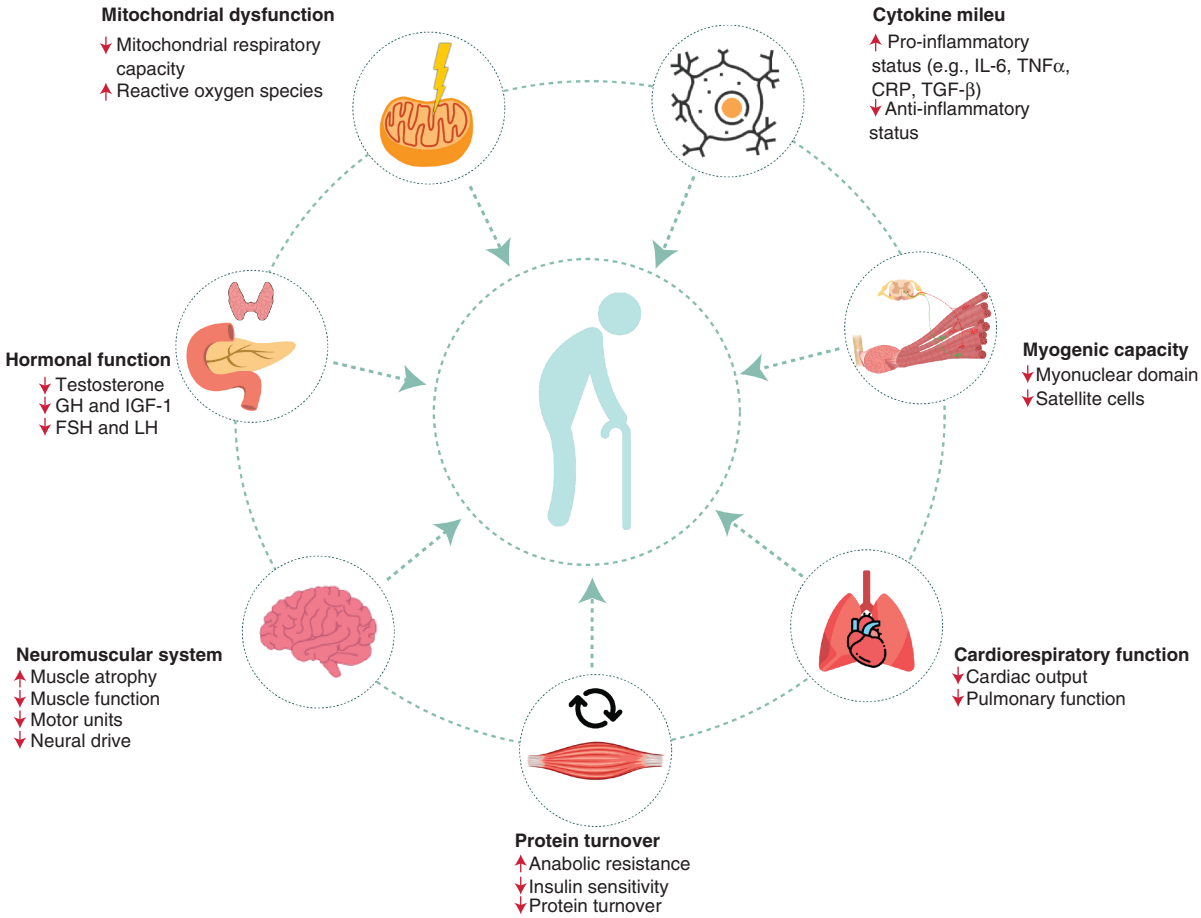


Figure 3 Main physiological changes leading to loss of muscle mass and functional decline in the oldest old. Abbreviations: CRP, C-reactive protein; FSH, follicle stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor; IL, interleukin; LH, luteinizing hormone; TFG-β, transforming growth factor β; TNFα, tumor necrosis factor α.

below for details). However, several other factors contribute to the age-related loss of muscle function (see Larsson et al. (157) for a review), which include quantitative and qualitative changes in muscle mass (i.e., not only loss of total muscle mass but also reduced muscle strength per unit muscle mass), together with alterations in neuromuscular function (1).

At the neuromuscular level, aging is accompanied by a loss of α-motoneurons and incomplete reinnervation of previously denervated muscle fibers (1, 157). Indeed, a 39% decrease in the number of motor units of the *tibialis anterior* muscle has been reported in older compared to young individuals (aged 66 vs. 27 years, respectively), with a further decline in subjects aged 82 years (i.e., 61% reduction compared to the young adults) (187). Moreover, aging results in a decreased rate of axonal (or "axoplasmic") transport (i.e., the transport of proteins and other molecules to and from the neuron) and conduction velocity (157); and decreases in voluntary activation (146), motor unit firing rate (295) and in the excitability of spinal pathways (as reflected by a decreased H-reflex) (145) have also been reported in the elderly.

Structural muscle changes contribute to the loss of muscle function. Some studies have observed that aging is usually associated with intramuscular infiltration of noncontractile tissue (i.e., fat and collagen) (143, 302), which might result in a decreased specific force (i.e., force production capacity related to the quantity of muscle mass). Moreover, there is compelling evidence that aging results in muscle fiber atrophy, especially in fast-twitch fibers (206), as well as in a fast to slow shift in muscle fiber phenotype that in turn leads to a decreased maximal force and power production capacity (46, 77). However, disuse periods, which can be frequent in the oldest old (particularly during hospitalization/institutionalization), also result in a decline in muscle mass and function but promote the opposite effect to aging on muscle fiber type, that is, a slow to fast shift (46). Finally, some muscle architectural properties may also vary with aging. For instance, muscle thickness and pennation angle decrease as we age, at least in some muscles such as *vastus lateralis* (151, 152). The lower muscle volume observed in some muscles (e.g., *gastrocnemius medialis*) of older individuals compared to their younger controls might not only be due to the fact that the former have fewer and/or thinner muscle fibers (and therefore lower muscle cross-sectional area) but also to an age-associated reduction in fascicle length

(202, 278), which, in turn, can lead to a further loss in muscle force generation and shortening velocity (and, consequently, in power production capacity). In contrast, no changes in fascicle length have been observed with aging in the *vastus lateralis*, *triceps brachii,* or *gastrocnemius* muscles of women aged (from ages 20 to 79 years) (151).

Hormonal function

Aging is related to several changes in endocrine function [for a review, see Lamberts et al. (154)] that might also contribute to the age-associated loss of muscle mass and strength in the elderly, including decreased circulating levels of growth hormone (GH) and insulin-growth factor (IGF)-1 (65, 121, 142) together with decreases in GH-releasing hormone and somatostatin (199). Of note, the GH/IGF-1 axis activates the phosphatidylinositol 3 kinase/protein kinase B (AKT) pathway, thereby increasing muscle protein synthesis (MPS) through activation of mammalian target of rapamycin (mTOR) signaling while decreasing muscle protein breakdown (MPB) via inactivation of forkhead box O (FOXO) transcription factors (287). Aging also results in decreases in serum testosterone and adrenal androgens (a phenomenon known as "andropause" in men) (90, 249). Testosterone increases muscle mass and function through its stimulating effect on protein synthesis and intramuscular IGF-1 mRNA, and also through a decreasing effect on the inhibitory IGF binding protein 4 (137). A cross-sectional study with subjects aged 70 to 102 years showed an inverse relationship between total testosterone levels and muscle strength and physical performance (215), and low free testosterone levels have been related to a greater incidence of sarcopenia in men and women (303, 304). In turn, menopause results in an abrupt decrease in ovarian estrogen production together with a concomitant increase in the levels of luteinizing and follicle stimulating hormones, which increases the risk for loss of bone mineral density in women (233). On the other hand, several mechanisms might support a role of estrogens in muscle anabolism, including conversion of these hormones into testosterone, inhibitory effect on catabolic cytokines [e.g., interleukin (IL)1, IL-6, tumor necrosis factor (TNF)-α], and stimulation of GH secretion (137).

Cytokine milieu

Aging is characterized by immune changes with subsequent cytokine dysregulation, that is, decreases in anti-inflammatory cytokines (e.g., IL-10, transforming growth factor-β) and increases in pro-inflammatory cytokines (e.g., IL-1α, IL-6, TNF-α) or in nuclear factor κB [NF-κB] signaling, which results in a chronic low-grade inflammatory status known as "inflammaging" (229). Several processes trigger these pro-inflammatory pathways, including age-related redox imbalance, senescence, and impaired autophagy (229).

A modification in the cytokine milieu and the subsequent pro-inflammatory status contribute to several of the deleterious changes associated with the aging process [for a review, see Michaud et al. and Rea et al. (188, 229)]. Inflammation, and particularly TNF-α, is related to an increased muscle catabolism (232). Several studies have shown that higher blood levels of IL-6, C-reactive protein (CRP), and TNF-α are related to greater declines in muscle mass and strength in the elderly, suggesting a potential association with sarcopenia (246, 247). A pro-inflammatory status (as reflected by higher levels of CRP, IL-1, IL-6 and TNF-α) is also associated with an increased risk of osteoporosis (5, 149, 306). Moreover, an increased production of these pro-inflammatory cytokines is related to a greater risk of vascular and neurological conditions (188).

Mitochondrial dysfunction and oxidative stress

Aging is accompanied by a decline in mitochondrial function (216), with subsequent decreases and increases in mitochondrial respiratory capacity and ROS generation, respectively [for a review, see Sun et al. (275)]. Although moderate levels of ROS play an essential role in cellular function regulation, an uncontrolled production (together with the age-related reduction in antioxidant buffering mechanisms) contributes to the aging process through a higher oxidative stress (167). Excess levels of oxidative stress are indeed involved in several aging-related processes such as senescence and inflammation (275). For instance, higher levels of oxidative stress (as reflected by greater concentrations of serum protein carbonyl) are associated with higher levels of the pro-inflammatory cytokine IL-6 (75). Moreover, high concentrations of serum protein carbonyl are associated with lower levels of muscle strength, severe walking disability, and overall increased mortality risk in elderly individuals (125, 251, 252).

Myogenic capacity

Muscle fibers are large multinucleated cells, and each myonucleus controls a given volume of cytoplasm known as myonuclear domain. It has been traditionally accepted that the myonuclear domain remains constant independently of muscle changes, that is, new myonuclei arise from satellite cells during muscle hypertrophy, whereas some myonuclei are lost by apoptosis during atrophy (120). However, the notion of a constant myonuclear domain has been questioned in the last decade (116, 200). Some studies in animal models have shown that the age-related decrease in muscle size is accompanied by a reduction (albeit of lower relative magnitude) in the number of myonuclei, with subsequent decreases in myonuclear domain (38). Other authors suggest that myonuclear changes might be dependent on the muscle fiber phenotype, with an age-related decrease in the myonuclear domain for those muscles with a predominant slow-twitch phenotype such as the *soleus* muscle but no change in fast-twitch muscles such as the *plantaris* (34).

Moreover, the paradigm of a constant myonuclear domain has also been questioned by some studies using animal disuse models. For instance, Bruusgaard and Gundersen (39) observed no myonuclei loss despite a marked reduction (by ~50%) in fiber cross-sectional area and no reductions in nuclear number or DNA content in a model of muscle atrophy despite marked decreases (75%–80%) in muscle mass and cross-sectional area, resulting in an approximately 85% reduction of the myonuclear domain (250). Moreover, aging has been related to a decrease in satellite cells in humans, but also to a higher number of myonuclei per muscle area (136). Thus, the myonuclear domain and the number of satellite cells decrease with aging, which suggests a decline in myonuclear efficiency and a loss of regenerative function.

Protein turnover

Although numerous mechanisms can contribute to muscle wasting during aging, muscle atrophy eventually results from a mismatch between MPS and MPB, with nutrition and physical exercise being the main mediators of the balance between MPS and MPB. Specifically, the intake of dietary protein and physical exercise are powerful stimuli for MPS promotion (14), whereas insulin seems to suppress MPB (111).

The magnitude of the differences in basal MPS or MPB between healthy young and elderly individuals does not seem high enough to support a role in the muscle loss that occurs with aging (292), although it must be noted that an excessive pro-inflammatory status (e.g., during disease in frail elderly) might considerably rise basal MPB (72). However, a lower increase in MPS in response to nutrition (i.e., amino acid ingestion) and exercise is observed in the elderly compared to their younger peers (71, 153), a phenomenon known as "anabolic resistance". In addition, the former present with a blunted inhibition of MPB in response to insulin (298), which together with the impaired MPS response to nutrition and exercise contribute to age-related muscle atrophy.

It has been proposed that the aforementioned "anabolic resistance" phenomenon could be explained, at least partly, by both a suboptimal protein intake and an inactive lifestyle, which are frequent in this population segment (41, 257). For instance, two weeks of reduced mobility (i.e., by decreasing the number of steps by 76%) are enough to reduce postprandial MPS, insulin sensitivity, and muscle mass in healthy elderly individuals (33). Other physiological mechanisms—although yet to be confirmed—such as an impaired nutrient digestion/absorption and blood flow have also been proposed to contribute to a lower amino acid delivery to the muscle, which together with an impairment in mTOR pathway signaling, reduced ribosomal biogenesis and satellite cell content (and subsequently reduced myogenic capacity) and increased ROS production and pro-inflammatory status, might contribute to the imbalance in protein turnover that is commonly observed with aging [for a review, see Wilkinson et al. (299)].

Physical Assessment in the Oldest Old

Although aging is associated with a progressive degeneration of intrinsic capacity, the timely recognition of this phenomenon might enable implementation of interventions aiming at preventing (or at least attenuating) it. This section aims to provide the reader with information on the methods that are currently available for assessing the major components related to the physical domain of intrinsic capacity, which might also serve to analyze the effectiveness of interventions.

Muscle strength

The assessment of handgrip strength is arguably the most widely used (40) as well as the simplest and cheapest option for the evaluation of muscle strength in the oldest old, and specific recommendations for its standardized measurement are available elsewhere (236). According to the European Working Group on Sarcopenia in Older People (EWGSOP), grip strength values below 27 and 16 kg are considered low for men and women, respectively (70). Elderly people with low handgrip strength present with a worse intrinsic capacity and a greater risk of hospitalization than their stronger counterparts (228). This test has proven a good predictor of overall mortality in the general population (103) and particularly in the oldest old (166), being related to a higher incidence of both cardiovascular disease (CVD) and non-CVD mortality as well as to functional limitations (163). Meta-analytic evidence supports the validity of handgrip strength for the prediction of decline in cognition, mobility, functional status, and mortality in community-dwelling older people (234).

Other tests such as the leg or bench press test can also be used for the assessment of muscle strength in the oldest old (40). In turn, isometric torque methods for assessing upper or lower limb strength allow the measurement of peak forces and rate of force development and are useful in the research context (97). However, other more practical methods might be more feasible in the clinical setting, such as the chair stand test (20). This test, also considered a test of physical performance (20), is recommended by the EWGSOP for the assessment of muscle strength (70) and measures the amount of time needed for patients to rise from a seated position, return to the seated position, and rise again a specific number of times (usually five in the geriatric context) without using their arms. This test shows a strong correlation with the gait ability of elderly patients and is a valid predictor (cutoff score of 17 s for 5 repetitions) of lower limb limitation, death, and hospitalization events (52).

Muscle mass

Magnetic resonance imaging (MRI) and computed tomography (CT) are considered the gold standards for the assessment of muscle mass, but their feasibility in primary care is more questionable owing to economical and practical reasons (i.e.,

high equipment costs, lack of portability, and requirement of highly trained personnel) (20, 70). In this respect, dual-energy X-ray absorptiometry (DXA) has been proposed as a valid, low-radiation alternative for the routine clinical assessment of muscle mass in the elderly (20, 290). Thresholds of 20 and 15 kg (when unadjusted) or 7 and 6 kg/m^2 (when adjusted for height^2) of appendicular lean mass (i.e., the sum of the muscle mass of the four limbs) have been proposed as cutoff points for sarcopenia in men and women, respectively (70).

Bioelectrical impedance analysis (BIA) is an affordable method that requires no specialized staff and overcomes one of the main limitations of DXA, that is, its lack of portability. This technique estimates the quantity of fat and lean body mass based on the analysis of tissue electrical resistance. However, it relies on conversion equations based on population-specific reference values obtained with DXA (110). It is therefore important to standardize the assessment methodology and to define cutoff values for diagnostic purposes in each population (109, 110). In this regard, the EWGSOP (70) recommends the use of raw measures produced by BIA devices and their standardization with the cross-validated equation of Sergi et al. (254), which is specific for older (60–85 years) Caucasian adults. Yet, whether this equation is also valid in those aged >85 years remains unknown.

Another method that has been proposed when DXA is not available is anthropometrical assessment (20), which is the most widely used method in clinical practice according to a recent international survey showing that, among those clinicians who assess muscle mass in elderly patients, 58% use anthropometric data, 46% DXA, 23% BIA, and <20% ultrasonography, MRI, or CT (40). Although several anthropometric measures are available for routine assessment (notably, body mass index, calf or mid-upper arm circumference, skinfold thickness), calf circumference is the most popular one (40). Anthropometrical measurements are not accurate indicators of muscle mass (282), but a lower size of the calf (cutoff point <31 cm for calf circumference) is associated with a lower frailty index and more severe functional performance decrements in the oldest old (156), and for this reason it has been proposed as a useful diagnostic method in the absence of more complex methods (i.e., DXA, BIA, or MRI) (20, 70).

Finally, among several other methods available for the assessment of muscle mass/quality [for a review, see Tosato et al. (282)], muscle ultrasonography is emerging as a promising alternative (70, 282). According to a recent systematic review, muscle ultrasonography provides valid and reliable information on the muscle size of elderly individuals (205). The assessment of thigh muscles by means of ultrasonography has proven to predict the risk of functional decline, rehospitalization, and death in patients aged approximately 80 years on average, including those who are unable to walk (115), which highlights the tool's potential in bedridden hospitalized elderly patients. Moreover, recommendations for standardizing its measurement in elders have been recently proposed (214). Thus, ultrasonography appears as a valid, noninvasive, and practical tool for the assessment of muscle mass in the geriatric context (281).

Physical performance

Although muscle mass and strength are important health phenotypes at all ages and particularly during aging, physical performance has been defined as an integrative indicator of an individual's health status (70).

Several tests are available for the assessment of physical performance in the oldest old, including gait speed, the timed up and go (TUG) test, stair climbing, the short physical performance battery (SPPB), and others (40). The assessment of gait speed is the most popular method (i.e., used by 62% of clinicians according to a recent international survey) (40). This test is usually conducted over 4 m, needs no special equipment (just a stopwatch), and is recommended as a diagnostic tool for sarcopenia with a cutoff point of 0.8 m/s (70). A systematic review identified gait speed as a prognostic factor for disability, cognitive impairment, institutionalization, falls, and mortality in community-dwelling older people (138), and a pooled analysis including 34,485 community-dwelling elders confirmed its relationship with mortality (272). Thus, gait speed has been proposed as a quick, inexpensive, and reliable measure that should be included in comprehensive geriatric assessment (213).

The SPPB, which measures performance in three different tests (repeated chair stand test, time needed to walk a distance of 4 m two times, and a hierarchical standing balance test) with a 0 to 12 sum-score for all three tests combined (117), is also one of the most popular tests for assessing old people in both clinical and research settings (20). According to a recent meta-analysis that included 17 studies, the SPPB has proven a good predictor of all-cause mortality (211), and a prospective study that included 542 older adults showed its validity for identifying individuals at high risk of lower body functional limitations (285). Moreover, this test can be performed in hospitalized older patients (93), allowing the identification of the patients at high risk of poor outcomes (i.e., rehospitalization and death) after hospital discharge (291). Further, the SPPB is one of the tests proposed by the EWGSOP for the assessment of sarcopenia (with a cutoff score <8) (70).

The TUG test, in which patients have to rise from a chair, walk 3 m, turn around, walk back, and sit down again (222), is also recommended for assessing physical performance and sarcopenia (cutoff >20 s) (70), and a recent study confirmed its validity as a mortality predictor in patients aged approximately 77 years on average (23). However, the assessment of gait speed has proven more representative of the whole motor ability of frail patients than the TUG (150). Other tests available for the assessment of the oldest old are the 6-min walk distance (6MWD) or the 400-m walk test, which can be used to determine aerobic capacity (20) and are also feasible for the assessment of sarcopenia (cutoff >6 min for the completion of 400 m), or the stair climb power test, which has

proven valid to identify leg power impairments (18). Of note, although the aforementioned physical performance tests are feasible in the clinical setting and can predict negative outcomes, some of them have down sides in terms of routine evaluation, such as the need of long corridors (for the 6MWD and 400-m walk test) or the fact that they can be time-consuming (e.g., ~10 min for the SPPB). For this reason, the EWGSOP advises the assessment of gait speed for the routine evaluation of physical performance in the clinical setting (70).

Functional ability in activities of daily living

Functional decline in the oldest old can affect their ability to perform basic activities of daily living (ADLs) (181). ADL function has proven an independent risk factor of mortality and hospitalization in the elderly, as well as of duration of hospitalization and number of medical visits (124, 191, 201, 203). Moreover, the loss of ADL function during hospitalization is associated with a wide range of negative outcomes at discharge including long-term disability, rehospitalization, institutionalization, and mortality (32, 96, 131).

There are different methods for the assessment of ADL function, but the Katz scale and the Barthel index are arguably the most popular ones. The Katz ADL scale includes six items (eating, transferring from bed to chair, walking, using the toilet, bathing, and dressing), each of which is scored with 0 (= unable to perform the activity without complete help), 0.5 or 1.0 (= able to perform the activity with little help or without any help, respectively); then, the six individual items are summed resulting in a 0 to 6 score for each individual (140). In turn, the Barthel index assesses patients' independence to perform ten basic ADLs [eating, transferring from bed to chair, using the toilet, bathing/showering, personal hygiene (e.g., tooth brushing, shaving), dressing, walking, stair climbing, and bowel and bladder control] over the previous 24 to 48 h based on self-report, collateral information, and direct observation (179). Performance in these domains is rated by the level of assistance needed, with some ADLs weighting more than others (e.g., transferring and mobility score up to 15 points, whereas bathing scores just up to 5 points) and yielding a maximum total score of 100 points (179). It has been suggested that the Barthel index might offer a more nuanced picture of disability and is able to detect more subtle changes in functioning than the Katz index (122). Moreover, the former has been proposed as a good option for ADL assessment in long-term care because patients' disability is usually more severe and stable, whereas the Barthel index might be better suited to more acute settings such as hospitalization periods (122). However, both the Katz scale and the Barthel index have limited sensitiveness to measure small impairments or improvements in ADL function (i.e., "floor" and "ceiling" effect, respectively) (122). For this reason, a complementary index that assesses independence in eight more complex activities (i.e., using the phone, grocery shopping, preparing meals, housekeeping, laundering, using transportation, taking medications, and managing finances), known as "instrumental ADL", is available to measure less severe levels of disability (160).

Sarcopenia

The term sarcopenia [from the Greek, "*sarx*" (flesh) and "*penia*" (loss)] was originally proposed by Irwin Rosenberg to describe the age-related decrease in muscle mass (239). However, this definition has evolved over the last decades and now refers to a condition characterized by decreases in both muscle mass and function, and in the last European Consensus on definition and diagnosis of sarcopenia, muscle strength comes to the forefront as the main determinant (70).

It is estimated that sarcopenia affects approximately 5% to 13% of people aged 60 to 70 years, and the incidence reaches 11% to 50% for those aged 80 or above (119, 162). This condition increases the risk of falls (26) and results in impaired physical performance and reduced ability to perform ADLs (181), which, in turn, leads to a loss of independence and need for long-term care (9, 245). Moreover, it is associated with an increased risk for cardiometabolic and respiratory diseases (16, 31), cognitive impairment (53), and mortality (155). Sarcopenia also poses an important economic burden, as it increases the economic costs of hospitalization (266) as well as the overall health-care costs (190, 269).

The algorithm for diagnosing sarcopenia and quantifying its severity according to the EWGSOP is shown in Figure 4. The SARC-F, a self-reported five-item questionnaire in which patients express their limitations in muscle strength and their ability to walk, rise from a chair, and climb stairs, as well as their experiences with falls, is recommended to identify individuals with probable sarcopenia (181). Thereafter, in order to confirm the presence of sarcopenia, deficits in muscle strength can be assessed with the handgrip strength test (cutoff values <27 and 16 kg for men and women, respectively) or repeated chair stand measures (>15 s for 5 rises), whereas low muscle quality/quantity (<7.0 and 6.0 kg m^2 of appendicular lean mass for men and women, respectively) can be assessed by DXA, BIA, MRI, or CT. Low muscle strength and mass would already confirm the presence of sarcopenia, but several physical performance tests including the SPPB (<8 points) or walking 400 m in >6 m can be used for the diagnosis of severe sarcopenia (70).

Frailty

Frailty, defined as "*a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death*", has been identified as the most problematic expression of population aging (60, 194). Although this condition seems to overlap, at least partly, with sarcopenia, they are not synonyms: indeed, sarcopenia is a contributor to the development of physical frailty, whereas the latter is a much broader concept than sarcopenia. Thus,

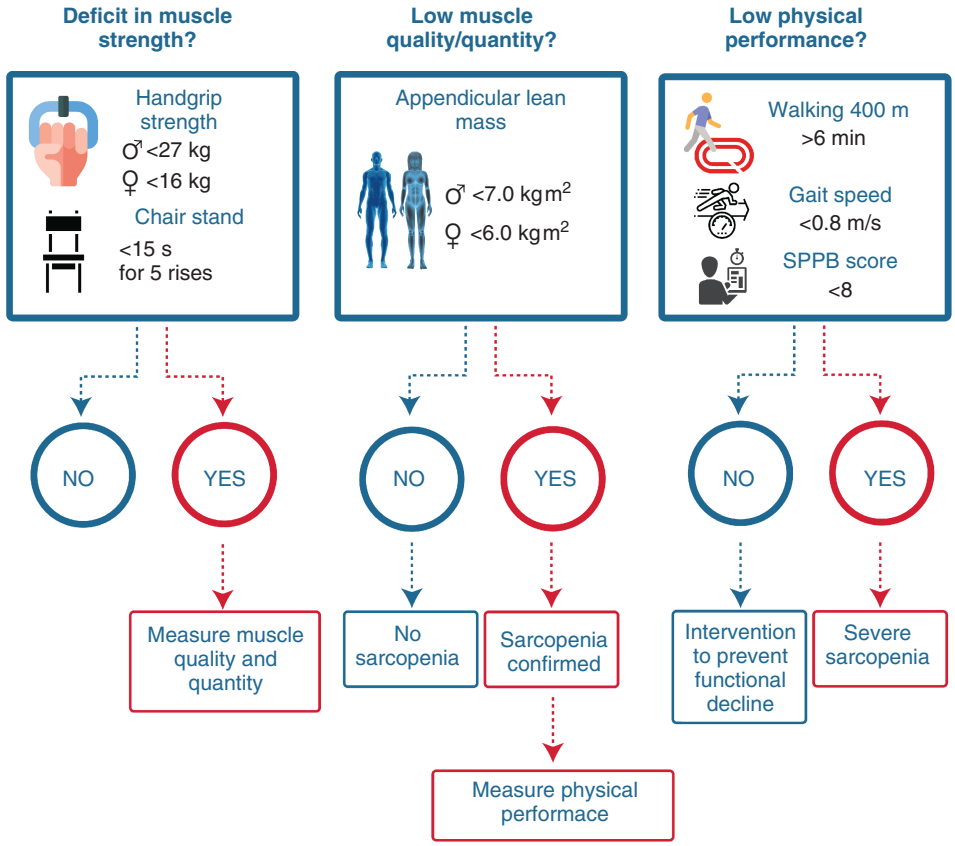


Figure 4 Algorithm for the diagnosis of sarcopenia and for the quantification of its severity proposed by the European Working Group on Sarcopenia in Older People (70), and available tests for its assessment. SPPB, short physical performance battery.

frailty is a multidimensional geriatric syndrome that refers to a decline in the physiological reserve of several systems (e.g., endocrine, immune, musculoskeletal) and results in negative consequences to physical, cognitive, and social dimensions (60) (Figure 5).

There are several methods for the diagnosis of frailty, but the Cardiovascular Health Study Frailty Screening Measure (99), also known as "frailty phenotype", is probably the most widely used. In this questionnaire, those individuals who meet three or more of the following criteria are considered frail: (i) weakness as measured by low handgrip strength (<~30 and 18 kg for men and women, respectively); (ii) slowness (low walking speed, i.e., time to walk 15 ft at usual pace > 6–7 s); (iii) low level of physical activity (i.e., hardly ever performing very energetic activities or even moderately energetic activities, equivalent to <383 and 270 kcal/week for men and women, respectively); (iv) low energy (self-reported exhaustion); and (v) unintentional weight loss (>4.5 kg in the previous year) [for specific details, see Fried et al. (99)]. Examples of some other popular validated methods for frailty assessment are the frailty index (134), the FRAIL questionnaire (195), the Clinical Frailty Scale (237), and the Gérontopôle Frailty Screening Tool (273). Given the wide heterogeneity in the definitions of frailty, the incidence of this condition has been reported to vary from 4% to 59% among people aged >65 years (63). In any case, it is important to note that the prevalence of frailty rises exponentially with age, for instance, increasing from 6.5% in individuals aged 60 to 69 years to 65% in those aged 90 and above (102).

Exercise for the Oldest Old

The sooner the better, but never too late

How we should preserve functional reserve across multiple systems to combat frailty and disability at an advanced age is a major challenge for modern medicine, which, at least up until now, cannot be resolved using drugs or drug combinations. In this respect, exercise appears as a potential solution (Figure 6).

There is strong scientific evidence that regular physical exercise throughout the life span is associated with healthy aging (74). As confirmed by a recent meta-analysis, chronically trained master athletes (both in endurance or strength/power sports) preserve their physical function at an advanced age (~70 years on average) (186). Moreover, almost no evidences of age-related degeneration in muscle properties (i.e., no changes in muscle size, fiber type or mitochondrial protein content) were observed in adults aged 55 to

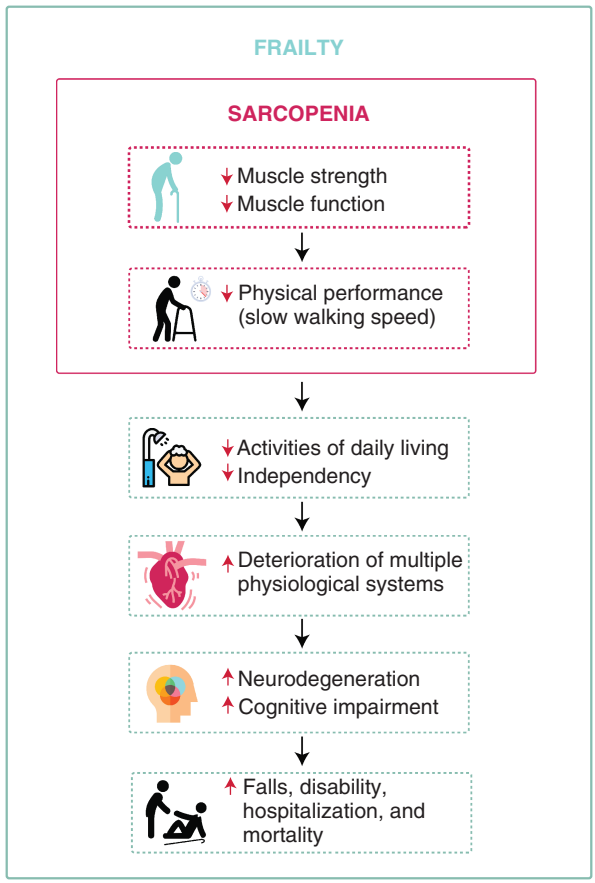


Figure 5 Overview of the relationship between sarcopenia, frailty, and overall functional decline in the elderly.

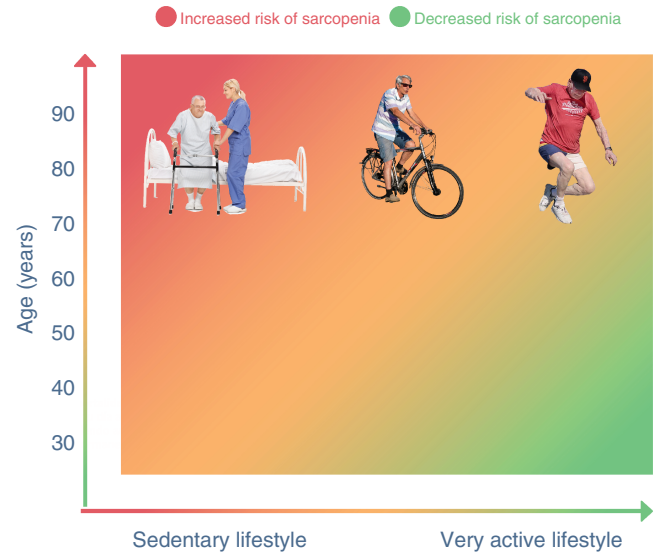


Figure 6 Relationship between the risk of functional/physiological decline during aging and the levels of physical activity.

79 years who had maintained high levels of aerobic exercise (cycling) during their lifetime (223). It has also been recently reported that lifelong aerobic exercise (50+ years) in people aged 70 and above attenuates Vo_{2peak} decline and prevents age-related reductions in muscle capillarization and aerobic enzyme activity, with these individuals having a skeletal muscle metabolic status similar to that of young exercisers and better than that of age-matched nonexercisers (112). Lifetime aerobic exercise has also been reported to mediate several aspects of senescence in immune cells (83). Thus, lifetime exercise is able to maintain many of the properties that are commonly affected by aging when accompanied by an inactive lifestyle (Figure 7).

Exercise is also beneficial for old people who are already physically impaired. A meta-analysis of 18 studies showed that physical exercise therapy improves mobility and physical functioning in community-dwelling elders who are physically frail and/or have physical disability and/or multimorbidity, with high-intensity programs eliciting the greatest gains (293). Meta-analytic evidence also supports the benefits of exercise on gait speed, balance, overall physical performance, and ADL function in frail elderly people (59, 108). Physical exercise appears as a potential intervention to preserve physiological reserve at the multisystem level (Figure 8). However, the type or magnitude of the benefits might differ depending on the type of exercise performed (Figure 9).

Main types of exercise

Resistance training

Resistance exercise training (RET) is based on movements performed against a specific external force, which is gradually increased, usually weight lifting but also exercising with resistance training machines or elastic bands. Several physiological mechanisms can explain, at least partly, the benefits of RET for the elderly [for a review, see Lavin et al. (159)]. This training modality elicits the activation of anabolic signaling pathways (e.g., Akt/mTOR pathway)—thereby stimulating MPS (73)—by increasing mechanical and metabolic stress (248, 305), which given the age-related impairment in protein turnover (see above for details) might help to attenuate the loss of muscle mass. Although RET induces hypertrophy across all fiber types its effect is more pronounced in fast-twitch fibers (24), which otherwise are more affected by aging-induced atrophy than slow-twitch ones (see above). RET interventions have also been proven to provide benefits at the neural level by reducing the rate of motor unit activation (i.e., myoelectrical activity) needed to perform a given task (128, 217), which together with the aforementioned benefits on muscle mass results in improved physical function. As a consequence, long-term participation in RET overall prevents age-related losses of muscle mass and strength as well as of bone mass [for review see Chodzko-Zajko et al. (57)].

A number of studies have confirmed the effectiveness of RET for the prevention of muscle wasting in the elderly, improving muscle strength through increases in both muscle volume and neural drive (91, 196, 230). RET [8–12 week training at 20%–70% of one-repetition maximum (1RM)] has

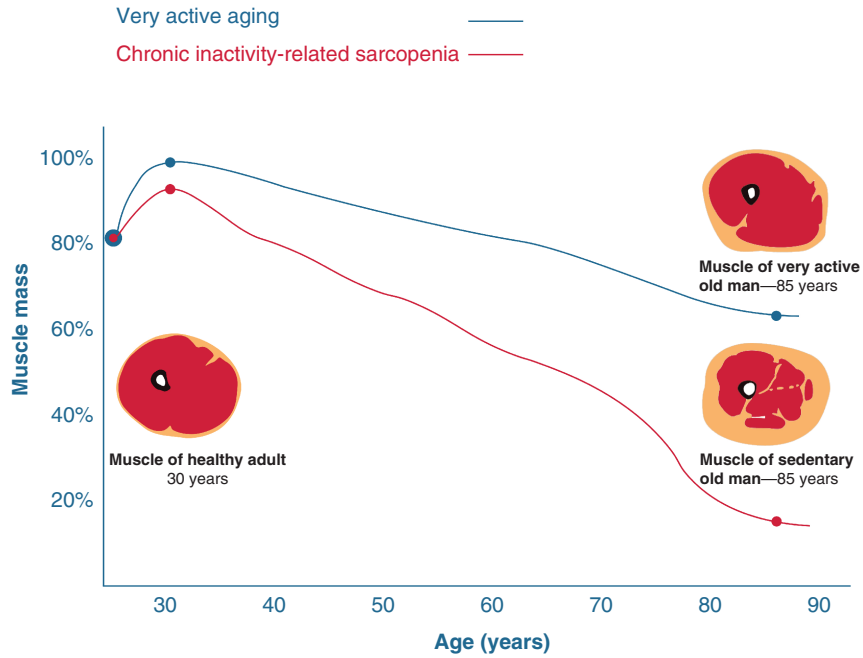


Figure 7 Representative example of the evolution of muscle mass during aging in a very active and a sedentary old man.

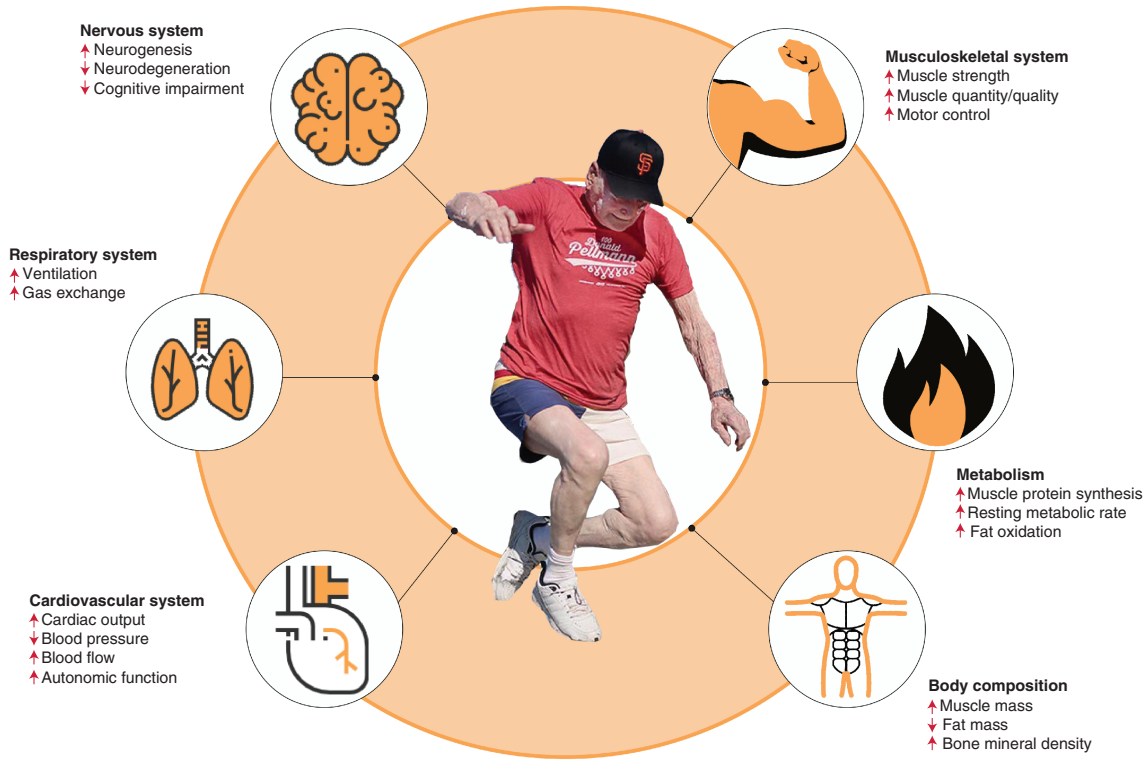


Figure 8 Overview of the multisystem exercise benefits in the oldest old.

been proven to increase muscle strength in institutionalized frail nonagenarians (43, 44, 255), and a recent meta-analysis showed the effectiveness of RET for improving muscle strength and power, as well as functional outcomes in physically frail oldest old people (aged 87 years on average) (171). Of note, no expensive materials are essentially needed for the implementation of RET programs in the elderly; for instance, the use of elastic bands has been reported to improve

Figure 9 Benefits of aerobic and resistance exercise in the elderly.

muscle strength and balance in institutionalized elders aged approximately 70 to 75 years on average (56, 197).

On the other hand, despite the importance of muscle strength preservation in the elderly, in this population segment loss of muscle power is a stronger predictor of functional disability than loss of muscle strength (231). In this respect, RET interventions including "high-speed" exercises (or at least the intention of moving fast) have proven feasible even in institutionalized oldest old frail individuals (mean age ~90 years) (43, 44) and seem to be more effective for the improvement of lower body muscle power and functionality in elders than traditional "low-speed" RET programs (227, 270, 283).

Aerobic exercise training

Aerobic exercise training (AET) is usually based on dynamic exercises of moderate intensity (~70% of Vo_{2peak} or ~80% of peak heart rate) involving large muscle groups [e.g., walking or brisk walking/jogging (in young participants) or cycle-ergometer training]. This exercise modality has been proven to counteract a major negative effect of aging, mitochondrial dysfunction (50) (see above), and although there are many overlapping pathways involved in the benefits of AET, a key player is the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) (132, 139). A recent preclinical study showed that decreases in PGC-1α expression mediate the muscle degeneration that normally occurs with aging, whereas increasing PGC-1α expression—which can be achieved with AET—seems to alleviate age-related muscle degeneration (105). The enhancing effect of AET on mitochondrial function results in improvements not only in oxidative capacity but also in redox status, which is of paramount importance during aging (see above) (29, 224). Moreover, AET increases the levels of heat shock proteins, a group of molecular chaperones that help to prevent skeletal muscle wasting through an improvement in MPS, inhibition of key atrophy signaling pathways (i.e., FOXO3a and NF-κB), and repair of damaged proteins (89, 253).

AET also induces several benefits on cardiovascular function (67). This training modality promotes skeletal muscle capillarization—which, as mentioned above, is impaired in the elderly—through increases in the mRNA and protein levels of vascular endothelial growth factor (104). It also improves endothelial function *via* increases in nitric oxide production and through the activation of PGC-1α (42, 279)—which exerts anti-inflammatory, antiatherogenic, and anti-inflammatory effects (e.g., it promotes the storage of fatty acids in adipose tissue thereby reducing their release to the blood) (54)—with subsequent protection against atherosclerotic heart disease and vascular aging (47). Moreover, AET attenuates aging-related autonomic dysfunction by increasing vagal tone to the heart while reducing sympathetic activity (193, 263), which might also contribute to lower CVD risk (263).

As a result of the aforementioned improvements in oxidative capacity and cardiovascular function, AET is considered the most effective type of exercise for the improvement of cardiorespiratory function (as typically reflected by increases in Vo_{2peak}) (57). Six months of AET enhanced Vo_{2peak} by approximately 19% in both young (24–32 years) and older individuals (60–82 years), together with increases in LV mass and early diastolic filling at rest and during exercise

(164). A 16-week AET program (3 sessions per week of cycle-ergometer exercise at 50%–85% of Vo_{2peak}) increased Vo_{2peak} (by ~16%) in adults aged 62 years on average while also inducing plasma volume expansion and improving LV systolic function (shortening and ejection fraction) (220). A 1-year AET program consisting of four sessions per week at 60% to 80% of Vo_{2peak} with brief high-intensity efforts proved beneficial for improving Vo_{2peak} (by ~26%) in individuals with a mean age of 64 years and also induced an increase in LV systolic function (86). Other studies have also shown the effectiveness of AET for increasing Vo_{2peak} in people aged 60 to 82 years (268, 271), and, indeed, this training modality seems to induce greater increases in Vo_{2peak} in older adults compared to RET (133).

Other Exercise Benefits

Benefits of exercise against neurodegeneration

There is evidence that regular physical exercise or PA in general is needed to maintain brain health over the life span (212). Of note, PA is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, whereas exercise usually involves more planned and structured activities (e.g., AET or RET). A meta-analysis of prospective studies found that physically active nondemented individuals had a 35% to 38% lower risk of cognitive decline than their inactive counterparts (264). Meta-analytic evidence also confirms the benefits of PA on some of the most common neurodegenerative conditions, notably Parkinson's disease (95, 258) and Alzheimer's disease (244). Further, PA has proven to attenuate cognitive function decline even in elderly individuals (mean age of 80 years) who already have dementia (114).

Although more research is needed regarding the specific mechanisms underlying exercise beneficial effects against age-induced neurodegeneration, some have been proposed. Exercise has been related to lower levels of biomarkers related to Alzheimer's disease such as plasma and brain β-amyloid (35, 165). Moreover, regular PA prevents the decreases that occur as we age on hippocampal volume (92), one of the major sites of neuroplasticity. A recent study showed that inducing hippocampal neurogenesis *per se* (whether pharmacologically or genetically) did not confer any benefit over markers of Alzheimer's disease in an animal model (58). By contrast, increases in hippocampal neurogenesis along with exercise-induced increases in the levels of brain-derived neurotrophic factor (BDNF) and reductions in β-amyloid load led to improvements in memory (58). Thus, hippocampal neurogenesis seems to ameliorate cognitive decline but only in the presence of an optimal brain environment (i.e., in the presence of neurotrophic factors such as BDNF) such as that induced by physical exercise (58).

In addition, contracting muscles produce a number of myokines (i.e., cytokines or small peptides that are released to the bloodstream), which in turn can induce several health benefits in the central nervous system (212), such as an improved neurotrophism (76). Particularly, BDNF levels are elevated by aerobic exercise in both healthy and demented individuals (61, 126). Exercise also seems to reduce pro-inflammatory conditions in the brain (66), which is important because inflammation is one of the pathophysiological mechanisms involved in the development of numerous neurodegenerative conditions such as Alzheimer's disease (161). Exercise also decreases oxidative stress in the long term (260), which is exacerbated in Alzheimer's disease and seems to play an important role in the etiology of this condition (240). Finally, regular physical exercise might attenuate the incidence of traditional CVD risk factors such as obesity, high blood pressure, hyperglycemia, and hypercholesterolemia, which in turn are associated with risk of Alzheimer's disease (226).

Benefits of exercise against cardiovascular diseases

Age is an independent CVD risk factor (301). The incidence of CVD has been estimated to increase from approximately 40% to 70% to 75% and 79% to 86% in those aged 40 to 59, 60 to 79, and ≥80 years, respectively (168). In this respect, it is important to note that CVD is currently the leading cause of mortality worldwide, with coronary heart disease and stroke accounting for approximately two-thirds of CVD deaths (168); and attending to the 2016 update of the American Heart Association, about two thirds of CVD deaths occur in people aged >75 years (198). Moreover, CVD seems to be associated with a higher risk of frailty (204) and imposes a tremendous burden in terms of mortality, disability, and health-care costs (301).

Several age-related conditions explain, at least partly, the greater incidence of CVD in the elderly compared to younger population segments, notably the increased stiffness of large vessels and the reductions in cardiac output (see above for further details in aging-related effects on the cardiovascular system) (174). However, physical exercise appears as an effective strategy for the prevention of CVD [for a review, see Fiuza-Luces et al. (94)].

Physical exercise attenuates the age-related decrease in Vo_{2peak} (see above for further details on the effects of exercise on cardiorespiratory function), which is of major clinical importance as cardiorespiratory fitness is a strong predictor of mortality and CVD risk (148, 182). Moreover, the above-mentioned exercise effects on body composition would also be beneficial given the role of obesity (particularly visceral fat mass accumulation) as a risk factor for CVD (78, 88). Low muscle strength, which can be prevented with RET (see above), has also been associated with a greater incidence of CVD (10), and indeed a recent prospective study with 0.5 million participants aged 40 to 69 years showed that a lower handgrip strength was related to a greater likelihood of CVD risk and CVD and all-cause mortality during a 7-year follow-up (51). Similarly, low muscle mass levels, which can also be increased by RET even at advanced ages (57),

have been associated with a higher risk of CVD and overall mortality in older adults (267).

Finally, other benefits of physical exercise that seem to mediate the reduction in CVD risk are its antiatherogenic effects (by improving vascular endothelial function and promoting structural vascular adaptations such as enlargement of conduit arteries, increases in the collagen and elastin content of atherosclerotic plaques, and development of collateral coronary vessels), the promotion of a healthy autonomic balance (increasing vagal tone to the heart thereby preventing malignant arrhythmias), and cardioprotection against ischemia–reperfusion injury (94). Moreover, the role of the working skeletal muscle as an endocrine organ able to secrete a myriad of myokines (e.g., irisin, IL-6, IL-15, fibroblast growth factor-21, and follistatin-related protein 1) with beneficial cardiovascular effects such as decreased inflammation, and improved metabolic homeostasis, thermogenesis or vasodilatation should not be disregarded (94).

Exercise in Disuse Situations

The levels of PA are usually low in the elderly, which is aggravated by the fact that numerous conditions common to this population segment can further increase their level of inactivity, particularly during hospitalization. Hospitalized elders spend indeed most of the time in bed even if they are able to walk independently (37), and nearly 75% of them do not walk at all during hospitalization (45).

Although muscle mass loss and functional decline are intrinsic features of aging, they can be also acutely exacerbated during disuse conditions (22). For instance, 10 days of bed rest result in a marked reduction in muscle mass and strength, walking speed, and functional ability in elderly people (mean age ~70 years) (62), and even shorter disuse periods are sufficient to elicit important negative consequences in these individuals, including a marked loss of muscle mass and strength, a suppression of MPS, and a slight increase in proteolytic markers (79, 277). Disuse situations such as hospitalization also affect glucose homeostasis in the elderly (25, 81, 184, 294). Moreover, hospitalization is associated with a greater risk of cognitive decline and incident dementia in nondemented elders (85). Further, the functional and cognitive decline that occurs during hospitalization periods can lead to the so-called hospital-associated disability, defined as the loss of ability to perform at least one basic ADL (i.e., bathing, dressing, rising from bed or a chair, using the toilet, eating, or walking across a room) independently at discharge (69). This condition occurs in more than one third of hospitalized adults over 70 years, especially in the presence of low mobility during hospital stay (68, 106, 107, 307, 308), and is associated with a wide range of negative outcomes, including long-term disability, institutionalization, or death (32, 96, 131).

Mechanisms underlying disuse-induced functional decline

The physiological mechanisms underlying disuse-related muscle wasting remain to be clearly elucidated, but several hypotheses have been proposed, notably mitochondrial dysfunction with subsequent increased ROS production, reduction in myogenic capacity (i.e., diminished total satellite cell content and function), and systemic inflammation (225, 274). Of note, while we wait for eventual mechanisms to be clearly identified, it should be kept in mind that muscle wasting is eventually a consequence of an imbalance between MPS and MPB [for a review, see Rudrappa et al. (242)]. In this respect, decreases in MPS seem to be the main determinants of muscle wasting during simple disuse situations (e.g., bed rest, limb immobilization, or physical inactivity) (218), but some "hypercatabolic" conditions (e.g., cancer-related cachexia, sepsis, burns, or critical illness that might lead to hypercortisolemia, hypoandrogenemia, or hypercytokinemia) can also induce an activation of proteolytic pathways (i.e., autophagy, ubiquitin-proteasome, or calpain and caspase systems) (30, 218, 219) (Figure 10). The disuse-induced suppression of anabolic signaling pathways—which is usually of higher magnitude in older than in young individuals—added to the abovementioned age-related anabolic resistance would

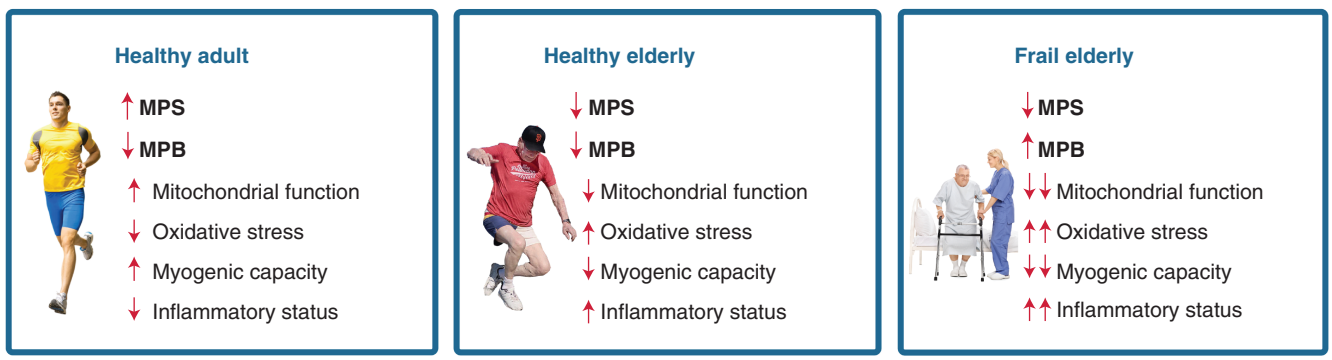


Figure 10 Relationship between muscle protein synthesis (MPS) and breakdown (MPB) in different conditions, and potential factors that influence this relationship.

maximize the deleterious effects of disuse *per se*. Lastly, disuse situations have also been reported to result in insulin resistance (25, 81), which would contribute to a reduced postprandial anabolic response and might potentially increase MPB during disuse situations (13). However, the effects of insulin resistance on MPB remain unknown (242).

Interventions to prevent functional decline during disuse situations

Different systematic reviews have concluded that exercise interventions are feasible and effective for the improvement of physical function in hospitalized elderly patients, with a meta-analysis of 17 trials showing that inhospital exercise programs improve functional status at discharge and reduce the likelihood of admission to nursing homes and mortality in geriatric patients (15). The inclusion of a simple intervention such as walking can maintain prehospitalization mobility in elderly individuals (mean age 75–80 years) (36, 209). However, the combination of walking together with strengthening exercises seems to provide greater benefits on functional ability (183, 259). Indeed, compared with usual hospital care, the inclusion of a program consisting of walking and stretching/strengthening exercises (e.g., leg lifts/swings, toe/heel raises) has been associated with a better ADL function at one month postdischarge in patients aged approximately 80 years on average (259). Further, a recent clinical trial showed that performing a multicomponent exercise program (combining walking, balance, and resistance exercises) during acute hospitalization (median duration of hospital stay of approximately 5 days) provided significant benefits in the functional ability of oldest old patients (mean age 87 years) during acute hospitalization (183).

Several physical interventions, including voluntary exercise or passive methods in case volitional exercise is not feasible, can be applied to prevent the functional decline associated with common disuse situations in the elderly such as hospitalization or bed rest (Figure 11) (284).

Resistance exercise training

RET is feasible in some disuse situations. A practical RET intervention including "conventional" exercises (e.g., single/bilateral leg extension, plantar/dorsiflexion) proved feasible during bed rest in elderly, acutely ill hospitalized patients aged 82 years on average (180). Isometric exercises (e.g., isometric leg press), which can be also performed during bed rest by institutionalized/hospitalized elderly patients, have proven effective for the prevention of muscle mass and strength losses (7, 141). Similarly, dynamic exercises (e.g., dynamic leg press) performed in bed are effective to prevent loss of muscle mass and strength during disuse periods (6, 8) and can attenuate the associated loss of bone mineral density (256). In turn, simple exercises are also feasible with elastic bands attached to the hospital bed, which can result in high levels of muscle activity (289) and eventually in improvements of muscle strength and balance in institutionalized elderly subjects (56, 197).

Aerobic exercise training

Although aging gradually decreases cardiorespiratory and oxidative capacity (see above for details), disuse situations elicit further, abrupt decreases (48). Notably, a longitudinal study demonstrated that 3 weeks of bed rest lead to a greater decline in Vo_{2peak} than 30 years of aging (185).

Given the abovementioned AET benefits on oxidative capacity and redox status, this training modality might reduce some of the negative consequences of disuse. AET has indeed proven to accelerate the recovery of functional capacity and strength in both young (20–27 years) and older adults (60–75 years) with leg immobilization (288). AET may be performed in hospital rooms or nursing homes with simple exercises such as step-ups, leg/arm stationary cycling, or walking along a corridor. In fact, a randomized controlled trial showed that this type of exercise can improve the muscle strength and functional capacity of critically ill adult patients [$n = 36$ (mean age 57 years) and $n = 31$ (56 years) in the control and intervention group, respectively]. Performing AET in supine position with a cycle ergometer or a treadmill placed in a vertical position can avoid cardiovascular deterioration in subjects submitted to 15 days of bed rest (296).

Blood flow restriction

Blood flow restriction (BFR), which is accomplished by inflating a cuff around the proximal part of a limb to a pressure that blocks venous blood return but not arterial inflow into the muscle rises anabolic hormones as a result of an increased metabolic stress (130, 276), ultimately facilitating MPS (101, 297). Meta-analytic evidence supports the effectiveness of BFR for increasing muscle mass and strength in the general population (169, 262), and the combination of low-load RET and BFR has proven effective for the prevention of muscle loss and weakness after one month of unilateral lower limb suspension in young/middle-aged adults (aged 18–50 years) (64). For this reason, it has been proposed that this strategy might also maximize training-induced adaptations when high-intensity RET is not feasible, such as in hospitalized/institutionalized elderly patients (284).

The combination of BFR and low-intensity exercise has proven to stimulate anabolic signaling pathways and improve muscle mass and strength in elderly subjects (100, 208, 300). Moreover, similar muscle mass gains have been observed in older individuals (~60–85 years) with high-intensity RET alone compared to low-intensity RET performed with BFR (286). Recent meta-analytical evidence shows indeed that the combination of BFR together with low-intensity RET (using elastic bands or weightlifting at <20% of 1RM, or low-intensity AET) is more effective than low-intensity RET alone for increasing muscle strength in clinical populations at risk of muscle wasting, such as the elderly (127). In addition,

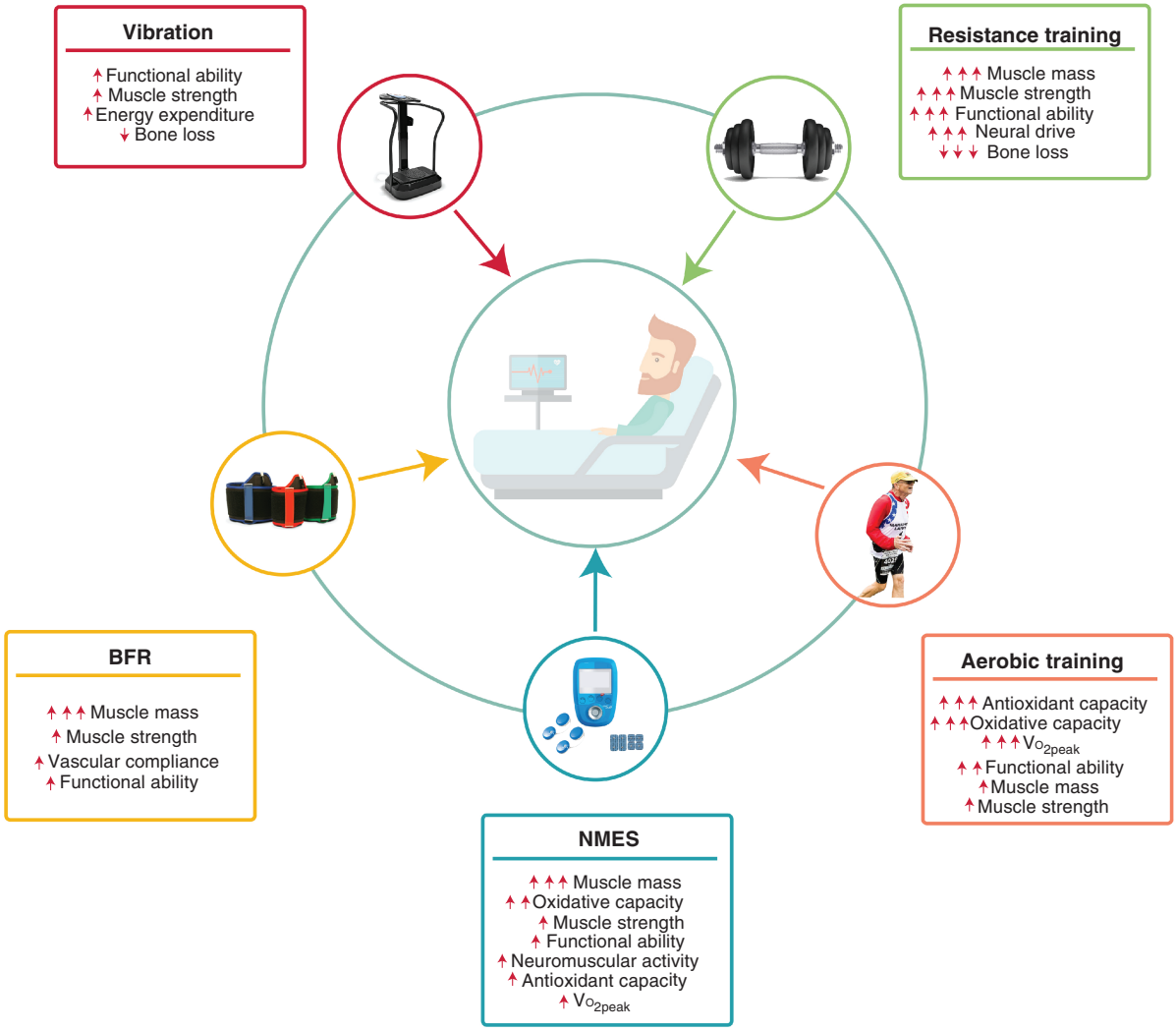


Figure 11 Physical interventions to prevent disuse-induced adaptations. Abbreviations: BFR, blood flow restriction; NMES, neuromuscular electrical stimulation; Vo_{2peak}, peak oxygen consumption.

BFR combined with light AET (e.g., walking) improves muscle size, strength, and functional ability in elderly people (3) and also enhances vascular compliance in this population (129, 208), which markedly decreases with aging and/or bed rest (27). Thus, although more evidence is needed regarding its effects in the oldest old, BFR in conjunction with low-intensity exercise training (AET or RET) is an effective strategy for attenuating muscle wasting and functional ability in those situations in which high-intensity exercise is not feasible.

Neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMES) generates involuntary muscle contractions through the application of high-intensity, intermittent electrical stimuli to skeletal muscles and is able to stimulate the same signaling pathways as those activated by voluntary exercise (12). In addition, electrically evoked contractions can activate corticomotor pathways similar to those activated by voluntary exercise (28, 98). For these reasons, there is biological rationale to support the use of NMES in those individuals who cannot perform volitional exercise (176, 210).

NMES has proven to counteract age-related muscle and functional decline in older people (144), with beneficial effects on muscle strength and functional ability also reported in prefrail and long-stay hospitalized people with a mean age >82 years (178, 189). A recent systematic review concluded that this strategy is effective for improving muscle mass/strength in adults at risk of muscle weakness with advanced disease (135). NMES has also proven beneficial during disuse situations in the general population, by increasing MPS while attenuating the loss of muscle mass, strength, and oxidative enzymatic capacity during bed rest and limb immobilization (80, 84). In addition, NMES has been reported to attenuate the loss of muscle mass and strength in adults

and elderly critically ill patients (177). Thus, there is growing evidence that NMES might be potentially effective during disuse situations, but further evidence is needed in oldest old patients.

Vibration

Vibration [i.e., application of a mechanical oscillation to the whole body (using a vibration platform) or some parts of it (using smaller vibrating devices)] has been proposed as a training modality with potential benefits in different clinical populations, including the frail elderly (235). This strategy promotes bone anabolism (241) and elicits involuntary muscle contractions through the activation of stretch reflexes (4, 87), which would make it useful during disuse situations.

Local vibration applied to the quadriceps muscles can help to prevent age-related loss of muscular strength, as confirmed in individuals aged 65 to 85 years (221). Moreover, performing exercise in combination with whole-body vibration (WBV) results in a higher increase in anabolic hormones (e.g., IGF-1) in elderly subjects than the same exercise alone (49). Moreover, WBV has proven safe, feasible, and effective for improving balance and mobility in nursing home residents aged approximately 80 years (17), and different systematic reviews and meta-analyses have concluded that WBV is effective to enhance muscle strength and balance in the elderly (158, 238, 261). Meta-analytic evidence also supports the role of this strategy for preventing bone loss in the lumbar spine of elderly women (175, 207), and it has been suggested that vibration might be more effective than walking to improve balance and hip bone mineral density in postmenopausal women (118). Thus, the vibratory stimulus alone or especially in combination with volitional exercise provides several benefits in the elderly. However, as most studies have applied both stimuli synchronously, in some cases it is difficult to discern the effects of vibration *per se*. Some studies have analyzed whether the addition of vibration to RET could provide additional benefits during immobilization periods compared to immobilization alone, and although the benefits on muscle mass are similar (192), the addition of vibration might provide greater benefits in terms of bone mineral density (21).

Conclusions

The oldest old are at high risk of intrinsic capacity decline (e.g., physical and cognitive impairment) with subsequent loss of independence. Age-related deterioration results from several physiological changes at the multisystemic level including endocrine, neuromuscular, metabolic, and cardiorespiratory impairment. In this respect, physical exercise provides multisystemic benefits and appears therefore as a means to counteract, at least partly, age decline in the physiological reserve of several systems/organs. Indeed, lifetime physical exercise can help to preserve (or at least attenuate the loss of) many of the properties affected by aging (e.g., cardiorespiratory fitness, muscle mass and strength, functional ability) and especially by inactive aging. Furthermore, benefits can also be obtained in the oldest old, including those who are frail, institutionalized, or hospitalized. Although more research is needed in this specific population segment, multicomponent exercise programs combining AET and RET should be routinely included in the lifestyle of the oldest old, particularly during disuse situations such as hospitalization. Finally, although different passive physical strategies such as NMES or vibration are available as a promising approach when volitional exercise is not feasible, more evidence is still needed to support their implementation.

Acknowledgements

P. L. Valenzuela is supported by a predoctoral contract granted by University of Alcalá (FPI2016). J. S. Morales is supported by a predoctoral contract granted by Spanish Ministry of Science, Innovation and Universities (Fondo de Investigaciones Sanitarias) and Sport (FPU14/03435). Research on research and aging by A. Lucia is supported by Spanish Ministry of Economy and Competitiveness and Fondos FEDER (PI15/00558 and PI18/00139). M. Izquierdo is supported by Spanish Ministry of Economy and competitiveness and Fondos FEDER (PI17/01814).

Disclosures

The authors declare no conflicts of interest.

References

1. Aagaard P, Suetta C, Caserotti P, Magnusson SP, Kjær M. Role of the nervous system in sarcopenia and muscle atrophy with aging: Strength training as a countermeasure. *Scand J Med Sci Sport* 20: 49-64, 2010.
2. Aalami O, Fang T, Song H, Nacamuli R. Physiological features of aging persons. *Arch Surg* 138: 1068-1076, 2003.
3. Abe T, Sakamaki M, Fujita S, Ozaki H, Sugaya M, Sato Y, Nakajima T. Effects of low-intensity walk training with restricted leg blood flow on muscle strength and aerobic capacity in older adults [Online]. *J Geriatr Phys Ther* 33: 34-40, 2010.
4. Abercromby AFJ, Amonette WE, Layne CS, Mcfarlin BK, Hinman MR, Paloski WH. Variation in neuromuscular responses during acute whole-body vibration exercise. *Med Sci Sports Exerc* 39: 1642-1650, 2007.
5. Abrahamsen B, Bonnevie-Nielsen V, Ebbesen EN, Gram J, Beck-Nielsen H. Cytokines and bone loss in a 5-year longitudinal study hormone replacement therapy suppresses serum soluble interleukin-6 receptor and increases interleukin-1-receptor antagonist: The Danish Osteoporosis Prevention Study. *J Bone Miner Res* 15: 1545-1554, 2000.
6. Akima H, Kubo K, Imai M, Kanehisa H, Suzuki Y, Gunji A, Fukunaga T. Inactivity and muscle: Effect of resistance training during bed rest on muscle size in the lower limb. *Acta Physiol Scand* 172: 269-278, 2001.
7. Akima H, Kubo K, Kanehisa H, Suzuki Y, Gunji A, Fukunaga T. Leg-press resistance training during 20 days of 6 degrees head-down-tilt bed rest prevents muscle deconditioning. *Eur J Appl Physiol* 82: 30-38, 2000.
8. Akima H, Ushiyama JI, Kubo J, Tonosaki SI, Itoh M, Kawakami Y, Fukuoka H, Kanehisa H, Fukunaga T. Resistance training during unweighting maintains muscle size and function in human calf. *Med Sci Sports Exerc* 35: 655-662, 2003.

9. Akune T, Muraki S, Oka H, Tanaka S, Kawaguchi H, Tokimura F, Yoshida H, Suzuki T, Nakamura K, Yoshimura N. Incidence of certified need of care in the long-term care insurance system and its risk factors in the elderly of Japanese population-based cohorts: The ROAD study. *Geriatr Gerontol* 14: 695-701, 2014.
10. Artero E, Lee D, Lavie C, España-Romero V, Church T, Blair S. Effects of muscular strength on cardiovascular risk factors and prognosis. *J Cardiopulm Rehabil Prev* 32: 351-358, 2012.
11. Astrand I, Astrand P, Hallback I, Kilbom A. Reduction in maximal oxygen uptake with age. *J Appl Physiol* 35: 649-654, 1973.
12. Atherton PJ, Babraj J, Smith K, Singh J, Rennie MJ, Wackerhage H. Selective activation of AMPK-PGC-1α or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. *FASEB J* 19: 786-788, 2005.
13. Atherton PJ, Greenhaff PL, Phillips SM, Bodine SC, Adams CM, Lang CH. Control of skeletal muscle atrophy in response to disuse: clinical/preclinical contentions and fallacies of evidence. *Am J Physiol Endocrinol Metab* 311: E594-E604, 2016.
14. Atherton PJ, Smith K. Muscle protein synthesis in response to nutrition and exercise. *J Physiol* 590: 1049-1057, 2012.
15. Bachmann S, Finger C, Huss A, Egger M, Stuck AE, Clough-Gorr KM. Inpatient rehabilitation specifically designed for geriatric patients: Systematic review and meta-analysis of randomised controlled trials. *BMJ* 340: 1230, 2010.
16. Bahat G, Ilhan B. Sarcopenia and the cardiometabolic syndrome: A narrative review. *Eur Geriatr Med* 7: 220-223, 2016.
17. Bautmans I, Van Hees E, Lemper JC, Mets T. The feasibility of whole body vibration in institutionalised elderly persons and its influence on muscle performance, balance and mobility: A randomised controlled trial. *BMC Geriatr* 5: 1-8, 2005.
18. Bean JF, Kiely DK, LaRose S, Alian J, Frontera WR. Is stair climb power a clinically relevant measure of leg power impairments in at-risk older adults? *Arch Phys Med Rehabil* 88: 604-609, 2007.
19. Beard JR, Officer A, De Carvalho IA, Sadana R, Pot AM, Michel JP, Lloyd-Sherlock P, Epping-Jordan JE, Peeters GMEE, Mahanani WR, Thiyagarajan JA, Chatterji S. The World report on ageing and health: A policy framework for healthy ageing. *Lancet* 387: 2145-2154, 2016.
20. Beaudart C, McCloskey E, Bruyère O, Cesari M, Rolland Y, Rizzoli R, Araujo de Carvalho I, Amuthavalli Thiyagarajan J, Bautmans I, Bertière MC, Brandi ML, Al-Daghri NM, Burlet N, Cavalier E, Cerreta F, Cherubini A, Fielding R, Gielen E, Landi F, Petermans J, Reginster JY, Visser M, Kanis J, Cooper C. Sarcopenia in daily practice: assessment and management. *BMC Geriatr* 16: 1-10, 2016.
21. Belavý DL, Beller G, Armbrecht G, Perschel FH, Fitzner R, Bock O, Börst H, Degner C, Gast U, Felsenberg D. Evidence for an additional effect of whole-body vibration above resistive exercise alone in preventing bone loss during prolonged bed rest. *Osteoporos Int* 22: 1581-1591, 2011.
22. Bell KE, von Allmen MT, Devries MC, Phillips SM. Muscle disuse as a pivotal problem in sarcopenia-related muscle loss and dysfunction. *J Frailty Aging* 5: 33-41, 2016.
23. Bergland A, Jørgensen L, Emaus N, Strand BH. Mobility as a predictor of all-cause mortality in older men and women: 11.8 year follow-up in the Tromsø study. *BMC Health Serv Res* 17: 1-7, 2017.
24. Bickel CS, Cross JM, Bamman M. Exercise dosing to retain resistance training adaptations in young and older adults. *Med Sci Sports Exerc* 43: 1177-1188, 2011.
25. Biensø RS, Ringholm S, Kiilerich K, Aachmann-Andersen NJ, Krogh-Madsen R, Guerra B, Plomgaard P, Van Hall G, Treebak JT, Saltin B, Lundby C, Calbet JAL, Pilegaard H, Wojtaszewski JFP. GLUT4 and glycogen synthase are key players in bed rest-induced insulin resistance. *Diabetes* 61: 1090-1099, 2012.
26. Bischoff-Ferrari HA, Orav JE, Kanis JA, Rizzoli R, Schlögl M, Staehelin HB, Willett WC, Dawson-Hughes B. Comparative performance of current definitions of sarcopenia against the prospective incidence of falls among community-dwelling seniors age 65 and older. *Osteoporos Int* 26: 2793-2802, 2015.
27. Bleeker MWP, de Groot PCE, Pawelczyk JA, Hopman MTE, Levine BD. Effects of 18 days of bed rest on leg and arm venous properties. *J Appl Physiol* 96: 840-847, 2004.
28. Blickenstorfer A, Kleiser R, Keller T, Keisker B, Meyer M, Riener R, Kollias S. Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. *Hum Brain Mapp* 30: 963-975, 2009.
29. Bo H, Jiang N, Ji LL, Zhang Y. Mitochondrial redox metabolism in aging: Effect of exercise interventions. *J Sport Health Sci* 2: 67-74, 2013.
30. Bodine S. Disuse-induced muscle wasting. *Int J Biochem Cell Biol* 45: 2200-2208, 2013.
31. Bone AE, Hepgul N, Kon S, Maddocks M. Sarcopenia and frailty in chronic respiratory disease: Lessons from gerontology. *Chron Respir Dis* 14: 85-99, 2017.
32. Boyd C, Landefeld C, Counsell S, Palmer R, Fortinsky R, Kresevic D, Burant C, Covinsky K. Recovery in activities of daily living among older adults following hospitalization for acute medical illness. *J Am Geriatr Soc* 56: 2171-2179, 2008.
33. Breen L, Stokes KA, Churchward-Venne TA, Moore DR, Baker SK, Smith K, Atherton PJ, Phillips SM. Two weeks of reduced activity decreases leg lean mass and induces "anabolic resistance" of myofibrillar protein synthesis in healthy elderly. *J Clin Endocrinol Metab* 98: 2604-2612, 2013.
34. Brooks NE, Schuenke MD, Hikida RS. Ageing influences myonuclear domain size differently in fast and slow skeletal muscle of rats. *Acta Physiol* 197: 55-63, 2009.
35. Brown BM, Peiffer JJ, Taddei K, Lui JK, Laws SM, Gupta VB, Taddei T, Ward VK, Rodrigues MA, Burnham S, Rainey-Smith SR, Villemagne VL, Bush A, Ellis KA, Masters CL, Ames D, MacAulay SL, Szoeke C, Rowe CC, Martins RN. Physical activity and amyloid-β plasma and brain levels: Results from the Australian imaging, biomarkers and lifestyle study of ageing. *Mol Psychiat.* 18: 875-881, 2013.
36. Brown CJ, Foley KT, Lowman JD, MacLennan PA, Razjouyan J, Najafi B, Locher J, Allman RM. Comparison of posthospitalization function and community mobility in hospital mobility program and usual care patients a randomized clinical trial. *JAMA Intern Med* 176: 921-927, 2016.
37. Brown CJ, Redden DT, Flood KL, Allman RM. The underrecognized epidemic of low mobility during hospitalization of older adults. *J Am Geriatr Soc* 57: 1660-1665, 2009.
38. Bruusgaard JC. Distribution of myonuclei and microtubules in live muscle fibers of young, middle-aged, and old mice. *J Appl Physiol* 100: 2024-2030, 2006.
39. Bruusgaard JC, Gundersen K. In vivo time-lapse microscopy reveals no loss of murine myonuclei during weeks of muscle atrophy. *J Clin Invest* 118: 1450-1457, 2008.
40. Bruyère O, Beaudart C, Reginster JY, Buckinx F, Schoene D, Hirani V, Cooper C, Kanis JA, Rizzoli R, McCloskey E, Cederholm T, Cruz-Jentoft A, Freiberger E. Assessment of muscle mass, muscle strength and physical performance in clinical practice: An international survey. *Eur Geriatr Med* 7: 243-246, 2016.
41. Burd NA, Gorissen SH, Van Loon LJC. Anabolic resistance of muscle protein synthesis with aging. *Exerc Sport Sci Rev* 41: 169-173, 2013.
42. Butcher LR, Thomas A, Backx K, Roberts A, Webb R, Morris K. Low-intensity exercise exerts beneficial effects on plasma lipids via pparγ. *Med Sci Sports Exerc* 40: 1263-1270, 2008.
43. Cadore EL, Casas-Herrero A, Zambom-Ferraresi F, Idoate F, Millor N, Gómez M, Rodriguez-Mañas L, Izquierdo M. Multicomponent exercises including muscle power training enhance muscle mass, power output, and functional outcomes in institutionalized frail nonagenarians. *Age (Omaha)* 36: 773-785, 2014.
44. Cadore EL, Moneo ABB, Mensat MM, Muñoz AR, Casas-Herrero A, Rodriguez-Mañas L, Izquierdo M. Positive effects of resistance training in frail elderly patients with dementia after long-term physical restraint. *Age (Omaha)* 36: 801-811, 2014.
45. Callen BL, Mahoney JE, Grieves CB, Wells TJ, Enloe M. Frequency of hallway ambulation by hospitalized older adults on medical units of an academic hospital. *Geriatr Nurs (Minneap)* 25: 212-217, 2004.
46. Canepari M, Pellegrino MA, D'Antona G, Bottinelli R. Single muscle fiber properties in aging and disuse. *Scand J Med Sci Sport* 20: 10-19, 2010.
47. Cannon RO. Role of nitric oxide in cardiovascular disease: Focus on the endothelium [Online]. *Clin Chem* 44: 1809-1819, 1998. http://clinchem.aaccjnls.org/content/clinchem/44/8/1809.full.pdf
48. Capelli C, Antonutto G, Kenfack MA, Cautero M, Lador F, Moia C, Tam E, Ferretti G. Factors determining the time course of $\dot{V}O_2$max decay during bedrest: Implications for $\dot{V}O_2$max limitation. *Eur J Appl Physiol* 98: 152-160, 2006.
49. Cardinale M, Soiza RL, Leiper JB, Gibson A, Primrose WR. Hormonal responses to a single session of wholebody vibration exercise in older individuals. *Br J Sports Med* 44: 284-288, 2010.
50. Cartee GD, Hepple RT, Bamman MM, Zierath JR. Exercise promotes healthy aging of skeletal muscle. *Cell Metab* 23: 1034-1047, 2016.
51. Celis-Morales CA, Welsh P, Lyall DM, Steell L, Petermann F, Anderson J, Iliodromiti S, Sillars A, Graham N, MacKay DF, Pell JP, Gill JMR, Sattar N, Gray SR. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: Prospective cohort study of half a million UK Biobank participants. *BMJ* 361: 1-10, 2018.
52. Cesari M, Kritchevsky SB, Newman AB, Eleanor M, Harris TB, Penninx BW, Brach JS, Tylavsky FA, Satterfield S, Bauer D, Rubin S, Visser M, Pahor M. Added value of physical performance measures in predicting adverse health-related events: Results from the health, aging, and body composition study. *J Am Geriatr Soc* 57: 251-259, 2009.
53. Chang KV, Hsu TH, Wu WT, Huang KC, Han DS. Association between sarcopenia and cognitive impairment: A systematic review and meta-analysis. *J Am Med Dir Assoc* 17: 1164.e7-1164.e15, 2016.

54. Cheang WS, Tian XY, Wong WT, Huang Y. The peroxisome proliferator-activated receptors in cardiovascular diseases: Experimental benefits and clinical challenges. *Br J Pharmacol* 172: 5512-5522, 2015.
55. Chistiakov DA, Sobenin IA, Revin VV, Orekhov AN, Bobryshev YV. Mitochondrial aging and age-related dysfunction of mitochondria. *Biomed Res Int* 2014, 2014.
56. Cho S-I, An D-H. Effects of a fall prevention exercise program on muscle strength and balance of the old–old elderly. *J Phys Ther Sci* 26: 1771-1774, 2014.
57. Chodzko-Zajko W, Proctor D, Singh M, Minson C, Nigg C, Salem G, Skinner J. Exercise and physical activity for older adults. *Med Sci Sports Exerc* 11: 1510-1530, 2009.
58. Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, Clemenson GD, Kim E, Rompala A, Oram MK, Asselin C, Aronson J, Zhang C, Miller SJ, Lesinski A, Chen JW, Kim DY, van Praag H, Spiegelman BM, Gage FH, Tanzi RE. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science (80-)* 361: eaan8821, 2018.
59. Chou CH, Hwang CL, Wu YT. Effect of exercise on physical function, daily living activities, and quality of life in the frail older adults: A meta-analysis. *Arch Phys Med Rehabil* 93: 237-244, 2012.
60. Clegg A, Young J, Iliffe S, Olde Rikkert M, Rockwood K. Frailty in elderly people. *Lancet* 381: 752-762, 2013.
61. Coelho FGDM, Vital TM, Stein AM, Arantes FJ, Rueda AV, Camarini R, Teodorov E, Santos-Galduróz RF. Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *J Alzheimers Dis* 39: 401-408, 2014.
62. Coker RH, Hays NP, Williams RH, Wolfe RR, Evans WJ. Bed rest promotes reductions in walking speed, functional parameters, and aerobic fitness in older, healthy adults. *Journals Gerontol—Ser A Biol Sci Med Sci* 70: 91-96, 2015.
63. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: A systematic review. *J Am Geriatr Soc* 60: 1487-1492, 2012.
64. Cook SB, Brown KA, DeRuisseau K, Kanaley JA, Ploutz-Snyder LL. Skeletal muscle adaptations following blood flow-restricted training during 30 days of muscular unloading. *J Appl Physiol* 109: 341-349, 2010.
65. Corpas E, Harman SM, Blackman MR. Human growth hormone and human aging. *Endocr Rev* 14: 20-39, 1993.
66. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends Neurosci* 30: 464-472, 2007.
67. Coudert J, Van Praagh E. Endurance exercise training in the elderly: Effects on cardiovascular function. *Curr Opin Clin Nutr Metab Care* 3: 479-483, 2000.
68. Covinsky KE, Palmer RM, Fortinsky RH, Counsell SR, Stewart AL, Kresevic D. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: Increased vulnerability with age. *J Am Geriatr Soc* 51: 451-458, 2003.
69. Covinsky KE, Pierluissi E, Story THEPS. Hospitalization-associated disability "she was probably able to ambulate, but I'm not sure". *JAMA* 306: 1782-1793, 2011.
70. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M, Bautmans I, Baeyens J-P, Cesari M, Cherubini A, Kanis J, Maggio M, Martin F, Michel J-P, Pitkala K, Reginster J-Y, Rizzoli R, Sánchez-Rodríguez D, Schols J. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 1-16, 48: 16-31, 2019.
71. Cuthbertson D. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. *FASEB J* 19: 422-424, 2005.
72. Dalle S, Rossmeislova L, Koppo K. The role of inflammation in age-related sarcopenia. *Front Physiol* 8: 1045, 2017.
73. Damas F, Phillips S, Vechin FC, Ugrinowitsch C. A review of resistance training-induced changes in skeletal muscle protein synthesis and their contribution to hypertrophy. *Sports Med* 45: 801-807, 2015.
74. Daskalopoulou C, Stubbs B, Kralj C, Koukounari A, Prince M, Prina AM. Physical activity and healthy ageing: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Res Rev* 38: 6-17, 2017.
75. Dayhoff-Brannigan M, Ferrucci L, Sun K, Fried LP, Walston J, Varadhan R, Guralnik JM, Semba RD. Oxidative protein damage is associated with elevated serum interleukin-6 levels among older moderately to severely disabled women living in the community. *Journals Gerontol—Ser A Biol Sci Med Sci* 63: 179-183, 2008.
76. Delezie J, Handschin C. Endocrine crosstalk between skeletal muscle and the brain. *Front Neurol* 9, 2018.
77. Deschenes MR. Effects of aging on muscle fibre type and size. *Sports Med* 34: 809-824, 2004.
78. Després JP. Body fat distribution and risk of cardiovascular disease: An update. *Circulation* 126: 1301-1313, 2012.
79. Dirks ML, Wall BT, Nilwik R, Weerts DHJM, Verdijk LB, van Loon LJC. Skeletal muscle disuse atrophy is not attenuated by dietary protein supplementation in healthy older men. *J Nutr* 144: 1196-1203, 2014.
80. Dirks ML, Wall BT, Snijders T, Ottenbros CLP, Verdijk LB, Van Loon LJC. Neuromuscular electrical stimulation prevents muscle disuse atrophy during leg immobilization in humans. *Acta Physiol* 210: 628-641, 2014.
81. Dirks ML, Wall BT, Van De Valk B, Holloway TM, Holloway GP, Chabowski A, Goossens GH, Van Loon LJ. One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. *Diabetes* 65: 2862-2875, 2016.
82. Dodds RM, Granic A, Davies K, Kirkwood TBL, Jagger C, Sayer AA. Prevalence and incidence of sarcopenia in the very old: Findings from the Newcastle 85+ Study. *J Cachexia Sarcopenia Muscle* 8: 229-237, 2017.
83. Duggal NA, Pollock RD, Lazarus NR, Harridge S, Lord JM. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. *Aging Cell* 17, 2018.
84. Duvoisin MR, Convertino VA, Buchanan P, Gollnick PD, Dudley GA. Characteristics and preliminary observations of the influence of electromyostimulation on the size and function of human skeletal muscle during 30 days of simulated microgravity. *Aviat Sp Env Med* 60: 671-678, 1989.
85. Ehlenbach WJ, Crane PK, Haneuse SJPA, Carson SS, Curtis JR, Larson EB. Association between acute care and critical illness hospitalization. *JAMA* 303: 763-770, 2010.
86. Ehsani AA, Ogawa T, Miller TR, Spina RJ, Jilka SM. Exercise training improves left ventricular systolic function in older men. *Circulation* 83: 96-103, 1991.
87. Falempin M, In-Albon SF. Influence of brief daily tendon vibration on rat soleus muscle in non-weight-bearing situation [Online]. *J Appl Physiol* 87: 3-9, 1999. http://www.ncbi.nlm.nih.gov/pubmed/10409551
88. Fan H, Li X, Zheng L, Chen X, Lan Q, Wu H, Ding X, Qian D, Shen Y, Yu Z, Fan L, Chen M, Tomlinson B, Chan P, Zhang Y, Liu Z. Abdominal obesity is strongly associated with cardiovascular disease and its risk factors in elderly and very elderly community-dwelling Chinese. *Sci Rep* 6: 1-9, 2016.
89. Feder ME, Hofmann GE. Heat-shock proteins, molecular chaperones, and the stress response: Evolutionary and ecological physiology. *Annu Rev Physiol* 61: 243-282, 1999.
90. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, Kinlay JBMC. Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab* 87: 589-598, 2002.
91. Ferri A, Scaglioni G, Pousson M, Capodaglio P, Van Hoecke J, Narici MV. Strength and power changes of the human plantar flexors and knee extensors in response to resistance training in old age. *Acta Physiol Scand* 177: 69-78, 2003.
92. Firth J, Stubbs B, Vancampfort D, Schuch F, Lagopoulos J, Rosenbaum S, Ward PB. Effect of aerobic exercise on hippocampal volume in humans: A systematic review and meta-analysis. *Neuroimage* 166: 230-238, 2018.
93. Fisher S, Ottenbacher KJ, Goodwin JS, Graham JE, Ostir GV. Short physical performance battery in hospitalized older adults. *Aging Clin Exp Res* 21: 445-452, 2009.
94. Fiuza-Luces C, Santos-Lozano A, Joyner M, Carrera-Bastos P, Picazo O, Zugaza J, Izquierdo M, Ruilope L, Lucia A. Exercise benefits in cardiovascular disease: Beyond attenuating traditional risk factors. *Nat Rev Cardiol* 15: 731-743, 2018.
95. Flach A, Jaegers L, Krieger M, Bixler E, Kelly P, Weiss EP, Ahmad SO. Endurance exercise improves function in individuals with Parkinson's disease: A meta-analysis. *Neurosci Lett* 659: 115-119, 2017.
96. Fortinsky RH, Covinsky KE, Palmer RM, Landefeld CS. Effects of functional status changes before and during hospitalization on nursing home admission of older adults. *J Gerontol – Ser A Biol Sci Med Sci* 54: 521-526, 1999.
97. Francis P, Toomey C, Mc Cormack W, Lyons M, Jakeman P. Measurement of maximal isometric torque and muscle quality of the knee extensors and flexors in healthy 50- to 70-year-old women. *Clin Physiol Funct Imag* 37: 448-455, 2017.
98. Francis S, Lin X, Aboushoushah S, White TP, Phillips M, Bowtell R, Constantinescu CS. fMRI analysis of active, passive and electrically stimulated ankle dorsiflexion. *Neuroimage* 44: 469-479, 2009.
99. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: Evidence for a phenotype. *Journals Gerontol Ser A Biol Sci Med Sci* 56: M146-M157, 2001.
100. Fry CS, Glynn EL, Drummond MJ, Timmerman KL, Fujita S, Abe T, Dhanani S, Volpi E, Rasmussen BB. Blood flow restriction exercise

stimulates mTORC1 signaling and muscle protein synthesis in older men. *J Appl Physiol* 108: 1199-1209, 2010.
101. Fujita S, Abe T, Drummond MJ, Cadenas JG, Dreyer HC, Sato Y, Volpi E, Rasmussen BB. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J Appl Physiol* 103: 903-910, 2007.
102. Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. *Age Ageing* 44: 162-165, 2015.
103. García-Hermoso A, Cavero-Redondo I, Ramírez-Vélez R, Ruiz JR, Ortega FB, Lee DC, Martínez-Vizcaíno V. Muscular strength as a predictor of all-cause mortality in an apparently healthy population: A systematic review and meta-analysis of data from approximately 2 million men and women. *Arch Phys Med Rehabil* 99: 2100-, 2018.
104. Gavin TP, Ruster RS, Carrithers JA, Zwetsloot KA, Kraus RM, Evans CA, Knapp DJ, Drew JL, McCartney JS, Garry JP, Hickner RC, No difference in the skeletal muscle angiogenic response to aerobic exercise training between young and aged men. *J Physiol* 585: 231-239, 2007.
105. Gill JF, Santos G, Schnyder S, Handschin C. PGC-1α affects aging-related changes in muscle and motor function by modulating specific exercise-mediated changes in old mice. *Aging Cell* 17: 1-13, 2018.
106. Gill TM, Allore HG, Gahbauer E, Murphy T. Change in disability after hospitalization or restricted activity in older persons. *JAMA* 304: 1919-1928, 2010.
107. Gill TM, Allore HG, Holford TR, Guo Z. Hospitalization, restricted activity, and the development of disability among older persons. *JAMA* 292: 2115-2124, 2004.
108. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, Sitjà-Rabert M, Salvà A. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: A systematic review and meta-analysis. *Arch Phys Med Rehabil* 95, 2014.
109. Gonzalez MC, Barbosa-Silva TG, Heymsfield SB. Bioelectrical impedance analysis in the assessment of sarcopenia. *Curr Opin Clin Nutr Metab Care* 21: 1, 2018.
110. Gonzalez MC, Heymsfield SB. Bioelectrical impedance analysis for diagnosing sarcopenia and cachexia: What are we really estimating? *J Cachexia Sarcopenia Muscle* 8: 187-189, 2017.
111. Greenhaff PL, Karagounis LG, Peirce N, Simpson EJ, Hazell M, Layfield R, Wackerhage H, Smith K, Atherton P, Selby A, Rennie MJ. Disassociation between the effects of amino acids and insulin on signaling, ubiquitin ligases, and protein turnover in human muscle. *Am J Physiol Endocrinol Metab* 295: E595-E604, 2008.
112. Gries KJ, Raue U, Perkins RK, Lavin KM, Overstreet BS, D'Acquisto LJ, Graham B, Finch WH, Kaminsky LA, Trappe TA, Trappe S. Cardiovascular and skeletal muscle health with lifelong exercise. *J Appl Physiol* 125: 1636-1645, 2018.
113. Groen B, Hamer HM, Snijders T, van Kranenburg J, Frijns D, Vink H, van Loon LJC. Skeletal muscle capillary density and microvascular function are compromised with aging and type 2 diabetes. *J Appl Physiol* 116: 998-1005, 2014.
114. Groot C, Hooghiemstra AM, Raijmakers PGHM, van Berckel BNM, Scheltens P, Scherder EJA, van der Flier WM, Ossenkoppele R. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing Res Rev* 25: 13-23, 2016.
115. Guerreiro AC, Tonelli AC, Orzechowski R, Dalla Corte RR, Moriguchi EH, de Mello RB. Bedside ultrasound of quadriceps to predict rehospitalization and functional decline in hospitalized elders. *Front Med* 4, 2017.
116. Gundersen K, Bruusgaard JC. Nuclear domains during muscle atrophy: Nuclei lost or paradigm lost? *J Physiol* 586: 2675-2681, 2008.
117. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: Assocation with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol Med Sci* 49: M85-M94, 1994.
118. Gusi N, Raimundo A, Leal A. Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: A randomized controlled trial. *BMC Musculoskelet Disord* 7: 1-8, 2006.
119. von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: Facts and numbers on prevalence and clinical impact. *J Cachexia Sarcopenia Muscle* 1: 129-133, 2010.
120. Hall ZW, Ralston E. Nuclear domains in muscle cells. *Cell* 59: 771-772, 1989.
121. Hameed M, Harridge SDR, Goldspink G. Sarcopenia and hypertrophy: A role for insulin-like growth factor-1 in aged muscle? *Exerc Sport Sci Rev* 30: 15-19, 2002.
122. Hartigan I. A comparative review of the Katz ADL and the Barthel Index in assessing the activities of daily living of older people. *Int J Older People Nurs* 2: 204-212, 2007.
123. He W, Goodkind D, Kowal P. *U.S. Census Bureau, International Population Reports*. Washington, DC: U.S. Government Publishing Office, 2016.
124. Hennessy S, Kurichi JE, Pan Q, Streim JE, Bogner HR, Xie D, Stineman MG. Disability stage is an independent risk factor for mortality in medicare beneficiaries aged 65 years and older. *PM R* 7: 1215-1225, 2015.
125. Howard C, Ferrucci L, Sun K, Freied L, Walston J, Varadhan R, Guralnik JM, Semba RD. Oxidative protein damage is associated with poor grip strength among older women living in the community. *J Appl Physiol* 103: 17-20, 2007.
126. Huang T, Larsen KT, Ried-Larsen M, Møller NC, Andersen LB. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. *Scand J Med Sci Sport* 24: 1-10, 2014.
127. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: A systematic review and meta-analysis. *Br J Sports Med* 51: 1003-1011, 2017.
128. Hunter GR, Treuth MS, Weinsier RL, Kekes-Szabo T, Kell SH, Roth DL, Nicholson C. The effects of strength conditioning on older women's ability to perform daily tasks. *J Am Geriatr Soc* 43: 756-760, 1995.
129. Iida H, Nakajima T, Kurano M, Yasuda T, Sakamaki M, Sato Y, Yamasoba T, Abe T. Effects of walking with blood flow restriction on limb venous compliance in elderly subjects. *Clin Physiol Funct Imaging* 31: 472-476, 2011.
130. Inagaki Y, Madarame H, Neya M, Ishii N. Increase in serum growth hormone induced by electrical stimulation of muscle combined with blood flow restriction. *Eur J Appl Physiol* 111: 2715-2721, 2011.
131. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. *JAMA* 279: 1187-1198, 1998.
132. Irrcher I, Adhihetty PJ, Joseph AM, Ljubicic V, Hood DA. Regulation of mitochondrial biogenesis in muscle by endurance exercise. *Sports Med* 33: 783-793, 2003.
133. Izquierdo M, Ibañez J, Häkkinen K, Kraemer WJ, Larrión JL, Gorostiaga EM. Once weekly combined resistance and cardiovascular training in healthy older men. *Med Sci Sports Exerc* 36: 435-443, 2004.
134. Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *J Am Geriatr Soc* 52: 1929-1933, 2004.
135. Jones S, Man William DC, Gao W, Higginson Irene J, Wilcock A, Maddocks M. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane Database Syst Rev* 10: CD009419, 2016.
136. Kadi F, Charifi N, Denis C, Lexell J. Satellite cells and myonuclei in young and elderly women and men. *Muscle Nerve* 29: 120-127, 2004.
137. Kamel HK, Maas D, Duthie EH. Role of hormones in the pathogenesis and management of sarcopenia. *Drugs Aging* 19: 865-877, 2002.
138. Kan GAVAN, Rolland Y, Andrieu S, Bauer J, Beauchet O, Bonnefoy M, Cesari M, Donini LM, Inzitari M, Nourhashemi F, Onder G, Ritz P, Salva A, Visser M, Vellas B. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. *J Nutr Health Aging* 13: 881-889, 2009.
139. Kang C, Ji LL. Role of PGC-1α in muscle function and aging. *J Sport Health Sci* 2: 81-86, 2013.
140. Katz S, Ford A, Moskowitz R, Jackson B, Jaffe M. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. *JAMA* 185: 914-918, 1963.
141. Kawakami Y, Akima H, Kubo K, Muraoka Y, Hasegawa H, Kouzaki M, Imai M, Suzuki Y, Gunji A, Kanehisa H, Fukunaga T. Changes in muscle size, architecture, and neural activation after 20 days of bed rest with and without resistance exercise. *Eur J Appl Physiol* 84: 7-12, 2001.
142. Kelijman M. Age-related alterations of the growth hormone/insulin-like-growth-factor I axis. *J Am Geriatr Soc* 39: 295-307, 1991.
143. Kent-Braun JA, Ng AV, Young K. Skeletal muscle contractile and non-contractile components in young and older women and men. *J Appl Physiol* 88: 662-668, 2000.
144. Kern H, Barberi L, Löfler S, Sbardella S, Burggraf S, Fruhmann H, Carraro U, Mosole S, Sarabon N, Vogelauer M, Mayer W, Krenn M, Cvecka J, Romanello V, Pietrangelo L, Protasi F, Sandri M, Zampieri S, Musaro A. Electrical stimulation (ES) counteracts muscle decline in seniors. *Front Aging Neurosci* 6: 1-11, 2014.
145. Kido A, Tanaka N, Stein RB. Spinal excitation and inhibition decrease as humans age. *Can J Physiol Pharmacol* 82: 238-248, 2004.
146. Klass M, Baudry S, Duchateau J. Voluntary activation during maximal contraction with advancing age: A brief review. *Eur J Appl Physiol* 100: 543-551, 2007.
147. Knudson R, Lebowitz M, Holberg C, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 127: 725-734, 1983.
148. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H, Satoru Kodama MD, PhD Kazumi Saito MD, PhD Shiro Tanaka, PhD Miho Maki, MS Yoko Yachi, RD, MS Mihoko Asumi, MS Ayumi Sugawara, RD Kumiko Totsuka, RD Hitoshi Shimano, MD, PhD Yasuo Ohashi,

PhD Nobuhiro Yamada, MD, PhD Hirohito Sone MD P. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events. *JAMA* 301: 2024-2035, 2009.
149. Koh JM, Khang YH, Jung CH, Bae S, Kim DJ, Chung YE, Kim GS. Higher circulating hsCRP levels are associated with lower bone mineral density in healthy pre- and postmenopausal women: Evidence for a link between systemic inflammation and osteoporosis. *Osteoporos Int* 16: 1263-1271, 2005.
150. Kubicki A. Functional assessment in older adults: Should we use timed up and go or gait speed test? *Neurosci Lett* 577: 89-94, 2014.
151. Kubo K, Kanehisa H, Azuma K, Ishizu M, Kuno S, Okada M, Funugaka T. Muscle architectural characteristics in women aged 20–79 years. *Med Sci Sports Exerc* 35: 39-44, 2003.
152. Kubo K, Kanehisa H, Azuma K, Ishizu M, Kuno SY, Okada M, Fukunaga T. Muscle architectural characteristics in young and elderly men and women. *Int J Sports Med* 24: 125-130, 2003.
153. Kumar V, Selby A, Rankin D, Patel R, Atherton P, Hildebrandt W, Williams J, Smith K, Seynnes O, Hiscock N, Rennie MJ. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. *J Physiol* 587: 211-217, 2009.
154. Lamberts S, van den Beld A, van der Lely A. The endocrinology of aging. *Science (80-)* 278: 419-424, 1997.
155. Landi F, Cruz-Jentoft AJ, Liperoti R, Russo A, Giovannini S, Tosato M, Capoluongo E, Bernabei R, Onder G. Sarcopenia and mortality risk in frail older persons aged 80 years and older: Results from iLSIRENTE study. *Age Ageing* 42: 203-209, 2013.
156. Landi F, Onder G, Russo A, Liperoti R, Tosato M, Martone AM, Capoluongo E, Bernabei R. Calf circumference, frailty and physical performance among older adults living in the community. *Clin Nutr* 33: 539-544, 2014.
157. Larsson L, Degens H, Li M, Salviati L, Lee Y il, Thompson W, Kirkland JL, Sandri M. Sarcopenia. Aging-related loss of muscle mass and function. *Physiol Rev* 99: 427-511, 2019.
158. Lau RWK, Liao LR, Yu F, Teo T, Chung RCK, Pang MYC. The effects of whole body vibration therapy on bone mineral density and leg muscle strength in older adults: A systematic review and meta-analysis. *Clin Rehabil* 25: 975-988, 2011.
159. Lavin KM, Roberts BM, Fry CS, Moro T, Rasmussen BB, Bamman MM. The importance of resistance exercise training to combat neuromuscular aging. *Physiology* 34: 112-122, 2019.
160. Lawton M, Brody E. Assessment of older people: Selfmaintaining and instrumental activities of daily living. *Gerontologist* 9: 179-186, 1969. Gerontologist 9: 1979–1986, 1969.
161. Lee YJ, Han SB, Nam SY, Oh KW, Hong JT. Inflammation and Alzheimer's disease. *Arch Pharm Res* 33: 1539-1556, 2010.
162. Legrand D, Vaes B, Matheï C, Swine C, Degryse JM. The prevalence of sarcopenia in very old individuals according to the european consensus definition: Insights from the belfrail study. *Age Ageing* 42: 727-734, 2013.
163. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A, Orlandini A, Seron P, Ahmed SH, Rosengren A, Kelishadi R, Rahman O, Swaminathan S, Iqbal R, Gupta R, Lear SA, Oguz A, Yusoff K, Zatonska K, Chifamba J, Igumbor E, Mohan V, Anjana RM, Gu H, Li W, Yusuf S. Prognostic value of grip strength: Findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* 386: 266-273, 2015.
164. Levy WC, Cerqueira MD, Abrass IB, Schwartz RS, Stratton JR. Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men. *Circulation* 88: 116-126, 1993.
165. Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM, Morris JC, Head D. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol* 68: 311-318, 2010.
166. Ling CHY, Taekema D, De Craen AJM, Gussekloo J, Westendorp RGJ, Maier AB. Handgrip strength and mortality in the oldest old population: The Leiden 85-plus study. *Cmaj* 182: 429-435, 2010.
167. Liochev SI. Reactive oxygen species and the free radical theory of aging. *Free Radic Biol Med* 60: 1-4, 2013.
168. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y. Heart disease and stroke statistics—2009 update. *Circulation* 119: 2009.
169. Loenneke JP, Wilson JM, Marín PJ, Zourdos MC, Bemben MG. Low intensity blood flow restriction training: A meta-analysis. *Eur J Appl Physiol* 112: 1849-1859, 2012.
170. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The Hallmarks of Aging. *Cell* 153: 1194-1217, 2013.
171. Lopez P, Pinto RS, Radaelli R, Rech A, Grazioli R, Izquierdo M, Cadore EL. Benefits of resistance training in physically frail elderly: a systematic review. *Aging Clin Exp Res* 30: 889-899, 2018.
172. Lowery EM, Brubaker AL, Kuhlmann E, Kovacs EJ. The aging lung. *Clin Interv Aging* 8: 1489-1496, 2013.
173. Lucca U, Tettamanti M, Logroscino G, Tiraboschi P, Landi C, Sacco L, Garrì M, Ammesso S, Bertinotti C, Biotti A, Gargantini E, Piedicorcia A, Nobili A, Pasina L, Franchi C, Djade CD, Riva E, Recchia A. Prevalence of dementia in the oldest old: The Monzino 80-plus population based study. *Alzheimers Dement* 11: 258-270.e3, 2015.
174. Lye M, Donnellan C. Heart disease in the elderly [Online]. *Heart* 84: 560-566, 2000. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1017783/
175. Ma C, Liu A, Sun M, Zhu H, Wu H. Effect of whole-body vibration on reduction of bone loss and fall prevention in postmenopausal women: A meta-analysis and systematic review. *J Orthop Surg Res* 11: 1-10, 2016.
176. Maffiuletti NA, Gondin J, Place N, Stevens-Lapsley J, Vivodtzev I, Minetto MA. Clinical use of neuromuscular electrical stimulation for neuromuscular rehabilitation: What are we overlooking? *Arch Phys Med Rehabil* 99: 806-812, 2018.
177. Maffiuletti NA, Roig M, Karatzanos E, Nanas S. Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: A systematic review. *BMC Med* 111, 2013.
178. Maggioni MA, Cè E, Rampichini S, Ferrario M, Giordano G, Veicsteinas A, Merati G. Electrical stimulation versus kinesitherapy in improving functional fitness in older women: A randomized controlled trial. *Arch Gerontol Geriatr* 50: e19-e25, 2010.
179. Mahoney F, Barthel D. Functional evaluation: The Barthel index. *Md State Med J* 14: 61-65, 1965.
180. Mallery L, MacDonald E, Hubley-Kozey C, Earl M, Rockwood K, MacKnight C. The feasibility of performing resistance exercise with acutely ill hospitalized older adults. *BMC Geriatr* 3: 1-18, 2003.
181. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: A symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle* 7: 28-36, 2016.
182. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. *JAMA Netw Open* 1: e183605, 2018.
183. Martínez-Velilla N, Casas-Herrero N, Zambon-Ferraresi F, López Sáez de Asteasu M, Lucia A, Galbete A, García-Baztán A, Alonso-Renedo J, González-Glaría B, Gonzalo-Lázaro M, Aspezteguía-Iraizoz I, Gutiérrez-Valencia M, Rodríguez-Mañas L, Izquierdo M. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern Med* 179: 28-36, 2019.
184. McGlory C, von Allmen MT, Stokes T, Morton RW, Hector AJ, Lago BA, Raphenya AR, Smith BK, McArthur AG, Steinberg GR, Baker SK, Phillips SM, Newman A. Failed recovery of glycemic control and myofibrillar protein synthesis with 2 wk of physical inactivity in overweight, prediabetic older adults. *J Gerontol Ser A*: 1-8, 2017.
185. Mcguire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the dallas bed rest and training study: I. effect of age on the cardiovascular response to exercise. *Circulation* 104: 1350-1357, 2001.
186. Mckendry J, Breen L, Shad BJ, Greig CA. Muscle morphology and performance in master athletes: A systematic review and meta-analyses. *Ageing Res Rev* 45: 62-82, 2018.
187. McNeil CJ, Doherty TJ, Stashuk DW, Rice CL. Motor unit number estimates in the tibialis anterior muscle of young, old, and very old men. *Muscle Nerve* 31: 461-467, 2005.
188. Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, Cesari M, Nourhashemi F. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc* 14: 877-882, 2013.
189. Mignardot JB, Deschamps T, Le Goff CG, Roumier FX, Duclay J, Martin A, Sixt M, Pousson M, Cornu C. Neuromuscular electrical stimulation leads to physiological gains enhancing postural balance in the pre-frail elderly. *Physiol Rep* 3: 1-18, 2015.
190. Mijnarends D, Luiking Y, Halfens R, Evers S, Lenaerts E, Verlaan S, Wallace M, Schols J, Meijers J. Muscle, health and costs: A glance at their relationship. *J Nutr Health Aging* 22: 766-773, 2018.
191. Millán-Calenti JC, Tubío J, Pita-Fernández S, González-Abraldes I, Lorenzo T, Fernández-Arruty T, Maseda A. Prevalence of functional disability in activities of daily living (ADL), instrumental activities of daily living (IADL) and associated factors, as predictors of morbidity and mortality. *Arch Gerontol Geriatr* 50: 306-310, 2010.
192. Miokovic T, Armbrecht G, Gast U, Rawer R, Roth HJ, Runge M, Felsenberg D, Belavý DL. Muscle atrophy, pain, and damage in bed rest reduced by resistive (Vibration) exercise. *Med Sci Sports Exerc* 46: 1506-1516, 2014.
193. Monahan KD, Dinenno FA, Tanaka H, Clevenger CM, Desouza CA, Seals DR. Regular aerobic exercise modulates age-associated declines in cardiovagal baroreflex sensitivity in healthy men. *J Physiol* 529: 263-271, 2000.

194. Morley J, Vellas B, van Kan G, Anker S, Bauer J, Bernabei R, Cesari M, Chumlea W, Doehner W, Evans J, Fried L, Guralnik J, Katz PR, Malmstrom TK, McCarter RJ, Gutierrez Robledo LM, Rockwood K, von Haehling S, Vandewoude MF, Walston J. Frailty consensus: A call to action John. *J Am Med Dir Assoc* 14: 392-397, 2013.
195. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging* 16: 601-608, 2012.
196. Morse CI, Thom JM, Mian OS, Muirhead A, Birch KM, Narici MV. Muscle strength, volume and activation following 12-month resistance training in 70-year-old males. *Eur J Appl Physiol* 95: 197-204, 2005.
197. Motalebi SA, Cheong LS, Iranagh JA, Mohammadi F. Effect of low-cost resistance training on lower-limb strength and balance in institutionalized seniors. *Exp Aging Res* 44: 48-61, 2018.
198. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, American Heart Association Statistics Committee, Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: A report from the American Heart Association. *Circulation* 133: e38-e360, 2016.
199. Muller EE, Rigamonti AE, Colonna VDG, Locatelli V, Berti F, Cella SG. GH-related and extra-endocrine actions of GH secretagogues in aging. *Neurobiol Aging* 23: 907-919, 2002.
200. Murach KA, Englund DA, Dupont-Versteegden EE, McCarthy JJ, Peterson CA. Myonuclear domain flexibility challenges rigid assumptions on satellite cell contribution to skeletal muscle fiber hypertrophy. *Front Physiol* 9: 1-7, 2018.
201. Na L, Pan Q, Xie D, Kurichi JE, Streim JE, Bogner HR, Saliba D, Hennessy S. Activity limitation stages are associated with risk of hospitalization among medicare beneficiaries. *PM R* 9: 433-443, 2017.
202. Narici MV, Maganaris CN, Reeves ND, Capodaglio P. Effect of aging on human muscle architecture. *J Appl Physiol* 95: 2229-2234, 2003.
203. Nascimento C de M, Oliveira C de, Firmo JOA, Lima-Costa MF, Peixoto SV. Prognostic value of disability on mortality: 15-year follow-up of the Bambuí cohort study of aging. *Arch Gerontol Geriatr* 74: 112-117, 2018.
204. Newman A, Gottdiener J, McBurnie M, Hirsch C, Kop W, Tracy R, Walston J, Fried L. Associations of subclinical cardiovascular disease with frailty [Online]. *J Gerontol – Ser A Biol Sci Med Sci* 56: 158-166, 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2001088257
205. Nijholt W, Scafoglieri A, Jager-Wittenaar H, Hobbelen JSM, van der Schans CP. The reliability and validity of ultrasound to quantify muscles in older adults: a systematic review. *J Cachexia Sarcopenia Muscle* 8: 702-712, 2017.
206. Nilwik R, Snijders T, Leenders M, Groen BBL, van Kranenburg J, Verdijk LB, Van Loon LJC. The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. *Exp Gerontol* 48: 492-498, 2013.
207. Oliveira L, Oliveira R, Pires-Oliveira D. Effects of whole body vibration exercises on bone mineral density in postmenopausal women: a systematic review and meta-analysis. *Osteoporos Int* 27: 2913-2933, 2016.
208. Ozaki H, Miyachi M, Nakajima T, Abe T. Effects of 10 weeks walk training with leg blood flow reduction on carotid arterial compliance and muscle size in the elderly adults. *Angiology* 62: 81-86, 2011.
209. Padula CA, Hughes C, Baumhover L. Impact of a nurse-driven mobility protocol on functional decline in hospitalized older adults. *J Nurs Care Qual* 24: 325-331, 2009.
210. Paillard T. Muscle plasticity of aged subjects in response to electrical stimulation training and inversion and/or limitation of the sarcopenic process. *Ageing Res Rev* 46: 1-13, 2018.
211. Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, Vaes B, Legrand D, Verghese J, Wang C, Stenholm S, Ferrucci L, Lai JC, Bartes AA, Espaulella J, Ferrer M, Lim JY, Ensrud KE, Cawthon P, Turusheva A, Frolova E, Rolland Y, Lauwers V, Corsonello A, Kirk GD, Ferrari R, Volpato S, Campo G. Short physical performance battery and all-cause mortality: Systematic review and meta-analysis. *BMC Med* 14: 1-9, 2016.
212. Pedersen BK. Physical activity and muscle–brain crosstalk. *Nat Rev Endocrinol*, 2019. https://www.ncbi.nlm.nih.gov/pubmed/30837717
213. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: A systematic review. *J Gerontol—Ser A Biol Sci Med Sci* 68: 39-46, 2013.
214. Perkisas S, Baudry S, Bauer J, Beckwée D, De Cock A-M, Hobbelen H, Jager-Wittenaar H, Kasiukiewicz A, Landi F, Marco E, Merello A, Piotrowicz K, Sanchez E, Sanchez-Rodriguez D, Scafoglieri A, Cruz-Jentoft A, Vandewoude M. Application of ultrasound for muscle assessment in sarcopenia: Towards standardized measurements. *Eur Geriatr Med*, 2018.
215. Perry HM, Miller DK, Patrick P, Morley JE. Testosterone and leptin in older African–American men: Relationship to age, strength, function, and season. *Metabolism* 49: 1085-1091, 2000.
216. Petersen KF, Morino K, Alves TC, Kibbey RG, Dufour S, Sono S, Yoo PS, Cline GW, Shulman GI. Effect of aging on muscle mitochondrial substrate utilization in humans. *Proc Natl Acad Sci* 112: 11330-11334, 2015.
217. Petrella JK, Kim JS, Tuggle SC, Bamman MM. Contributions of force and velocity to improved power with progressive resistance training in young and older adults. *Eur J Appl Physiol* 99: 343-351, 2007.
218. Phillips SM, Mcglory C. The dominant mechanism causing disuse muscle atrophy is decreased protein synthesis. *J Physiol* 592: 5341-5343, 2014.
219. Phillips SM, Glover EI, Rennie MJ. Alterations of protein turnover underlying disuse atrophy in human skeletal muscle. *J Appl Physiol* 107: 645-654, 2009.
220. Pickering GP, Fellmann N, Morio B, Ritz P, Amonchot A, Vermorel M, Coudert J. Effects of endurance training on the cardiovascular system and water compartments in elderly subjects. *J Appl Physiol* 83: 1300-1306, 1997.
221. Pietrangelo T, Mancinelli R, Toniolo L, Cancellara L, Paoli A, Puglielli C, Iodice P, Doria C, Bosco G, D'Amelio L, Di Tano G, Fulle S, Saggini R, Fano G, Reggiani C. Effects of local vibrations on skeletal muscle trophism in elderly people: Mechanical, cellular, and molecular events. *Int J Mol Med* 24: 503-512, 2009.
222. Podsiadlo D, Richardson S. The timed "Up & Go": A test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 39: 142-148, 1991.
223. Pollock RD, O'Brien KA, Daniels LJ, Nielsen KB, Rowlerson A, Duggal NA, Lazarus NR, Lord JM, Philp A, Harridge SDR. Properties of the vastus lateralis muscle in relation to age and physiological function in master cyclists aged 55–79 years. *Aging Cell* 17, 2018.
224. Powers SK, Talbert EE, Adhihetty PJ. Reactive oxygen and nitrogen species as intracellular signals in skeletal muscle. *J Physiol* 589: 2129-2138, 2011.
225. Powers SK, Wiggs MP, Duarte JA., Zergeroglu AM, Demirel HA. Mitochondrial signaling contributes to disuse muscle atrophy. *AJP Endocrinol Metab* 303: E31-E39, 2012.
226. Qiu C, Kivipelto M, Von Strauss E. Epidemiology of Alzhemer's disease: Occurrence, determinants, and strategies. *Dialogues Clin Neurosci* 11: 111-128, 2009.
227. Ramírez-Campillo R, Castillo A, de la Fuente CI, Campos-Jara C, Andrade DC, Álvarez C, Martínez C, Castro-Sepúlveda M, Pereira A, Marques MC, Izquierdo M. High-speed resistance training is more effective than low-speed resistance training to increase functional capacity and muscle performance in older women. *Exp Gerontol* 58: 51-57, 2014.
228. Ramírez-Vélez R, Correa-Bautista J, García-Hermoso A, Cano C, Izquierdo M. Reference values for handgrip strength and their association with intrinsic capacity domains among older adults. *J Cachexia Sarcopenia Muscle* 10: 278-286, 2019.
229. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Denis Alexander H, Ross OA. Age and age-related diseases: Role of inflammation triggers and cytokines. *Front Immunol* 9: 1-28, 2018.
230. Reeves ND, Narici MV, Maganaris CN. In vivo human muscle structure and function: Adaptations to resistance training in old age. *Exp Physiol* 89: 675-689, 2004.
231. Reid KF, Fielding R a. Skeletal muscle power: A critical determinant of physical functioning in older adults. *Exerc Sport Sci Rev* 40: 4-12, 2012.
232. Reid MB, Li YP. Tumor necrosis factor-α and muscle wasting: A cellular perspective. *Respir Res* 2: 269-272, 2001.
233. Riggs BL. Endocrine causes of age-related bone loss and osteoporosis [Online]. *Novartis Found Symp* 242: 244-247, 2002. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11855691
234. Rijk JM, Roos PRKM, Deckx L, Van den Akker M, Buntinx F. Prognostic value of handgrip strength in people aged 60 years and older: A systematic review and meta-analysis. *Geriatr Gerontol Int* 16: 5-20, 2016.
235. Rittweger J. Vibration as an exercise modality: How it may work, and what its potential might be. *Eur J Appl Physiol* 108: 877-904, 2010.
236. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, Sayer AA. A review of the measurement of grip strength in clinical and epidemiological studies: Towards a standardised approach. *Age Ageing* 40: 423-429, 2011.
237. Rockwood K, MacKnight C, Bergman H, Hogan D, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 173: 489-495, 2005.

238. Rogan S, Taeymans J, Radlinger L, Naepflin S, Ruppen S, Bruelhart Y, Hilfiker R. Effects of whole-body vibration on postural control in elderly: An update of a systematic review and meta-analysis. *Arch Gerontol Geriatr* 73: 95-112, 2017.
239. Rosenberg I. Summary comments. *Am J Clin Nutr* 50: 1231-1233, 1989.
240. Rottkamp CA, Nunomura A, Raina AK, Sayre LM, Perry G, Smith MA. Oxidative stress, antioxidants, and Alzheimer disease. *Alzheimer Dis Assoc Disord* 14: 62-66, 2000.
241. Rubin C, Turner S, Bain S, Mallinckrod C, McLeod K. Low mechanical signals strengthen long bones. *Nature* 412: 603-604, 2001.
242. Rudrappa SS, Wilkinson DJ, Greenhaff PL, Smith K, Idris I, Atherton PJ. Human skeletal muscle disuse atrophy: Effects on muscle protein synthesis, breakdown, and insulin resistance: A qualitative review. *Front Physiol* 7: 1-10, 2016.
243. Sander M, Oxlund B, Jespersen A, Krasnik A, Mortensen EL, Westendorp RGJ, Rasmussen LJ. The challenges of human population ageing. *Age Ageing* 44: 185-187, 2015.
244. Santos-Lozano A, Pareja-Galeano H, Sanchis-Gomar F, Quindós-Rubial M, Fiuza-Luces C, Cristi-Montero C, Emanuele E, Garatachea N, Lucia A. Physical activity and alzheimer disease: A protective association. *Mayo Clin Proc* 91: 999-1020, 2016.
245. dos Santos L, Cyrino ES, Antunes M, Santos DA, Sardinha LB. Sarcopenia and physical independence in older adults: The independent and synergic role of muscle mass and muscle function. *J Cachexia Sarcopenia Muscle* 8: 245-250, 2017.
246. Schaap L, Pluijm S, Deeg D, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am J Med* 119: 526.e9-526.e17, 2006.
247. Schaap LA, Pluijm SMF, Deeg DJH, Harris TB, Kritchevsky SB, Newman AB, Colbert LH, Pahor M, Rubin SM, Tylavsky FA, Visser M. Higher inflammatory marker levels in older persons: Associations with 5-year change in muscle mass and muscle strength. *J Gerontol – Ser A Biol Sci Med Sci* 64: 1183-1189, 2009.
248. Schoenfeld BJ. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sports Med* 43: 179-194, 2013.
249. Schulman C, Lunenfeld B. The ageing male. *World J Urol* 20: 4-10, 2002.
250. Schwartz LM, Brown C, McLaughlin K, Smith W, Bigelow C. The myonuclear domain is not maintained in skeletal muscle during either atrophy or programmed cell death. *Am J Physiol – Cell Physiol* 311: C607-C615, 2016.
251. Semba R, Ferrucci L, Sun K, Walswon J, Varadhan R, Guralnik J, Fried L. Oxidative stress and severe walking disability among older women. *Am J Med* 120: 1084-1089, 2007.
252. Semba RD, Ferrucci L, Sun K, Walston J, Varadhan R, Guralnik JM, Fried LP. Oxidative stress is associated with greater mortality in older women living in the community. *J Am Geriatr Soc* 55: 1421-1425, 2007.
253. Senf SM, Dodd SL, McClung JM, Judge AR. Hsp70 overexpression inhibits NF- B and Foxo3a transcriptional activities and prevents skeletal muscle atrophy. *FASEB J* 22: 3836-3845, 2008.
254. Sergi G, De Rui M, Veronese N, Bolzetta F, Berton L, Carraro S, Bano G, Coin A, Manzato E, Perissinotto E. Assessing appendicular skeletal muscle mass with bioelectrical impedance analysis in free-living Caucasian older adults. *Clin Nutr* 34: 667-673, 2015.
255. Serra-Rexach JA, Bustamante-Ara N, Hierro Villarán M, González Gil P, Sanz Ibáñez MJ, Blanco Sanz N, Ortega Santamaría V, Gutiérrez Sanz N, Marín Prada AB, Gallardo C, Rodríguez Romo G, Ruiz JR, Lucia A. Short-term, light- to moderate-intensity exercise training improves leg muscle strength in the oldest old: A randomized controlled trial. *J Am Geriatr Soc* 59: 594-602, 2011.
256. Shackelford LC, LeBlanc a D, Driscoll TB, Evans HJ, Rianon NJ, Smith SM, Spector E, Feeback DL, Lai D. Resistance exercise as a countermeasure to disuse-induced bone loss. *J Appl Physiol* 97: 119-129, 2004.
257. Shad BJ, Thompson JL, Breen L. Does the muscle protein synthetic response to exercise and amino acid-based nutrition diminish with advancing age? A systematic review. *Am J Physiol Endocrinol Metab* 311: E803-E817, 2016.
258. Shu HF, Yang T, Yu SX, Huang HD, Jiang LL, Gu JW, Kuang YQ. Aerobic exercise for Parkinson's disease: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 9, 2014.
259. Siebens H, Aronow H, Edwards D, Ghasemi Z. A randomized controlled trial of exercise to improve outcomes of acute hospitalization in older adults. *J Am Geriatr Soc* 48: 1545-1546, 2000.
260. Simioni C, Zauli G, Martelli AM, Vitale M, Sacchetti G, Gonelli A, Neri LM. Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging. *Oncotarget* 9: 17181-17198, 2018.
261. Sitjà-Rabert M, Rigau D, Fort Vanmeerghaeghe A, Romero-Rodríguez D, Bonastre Subirana M, Bonfill X. Efficacy of whole body vibration exercise in older people: A systematic review. *Disabil Rehabil* 34: 883-893, 2012.
262. Slysz J, Stultz J, Burr JF. The efficacy of blood flow restricted exercise: A systematic review & meta-analysis. *J Sci Med Sport* 19: 669-675, 2016.
263. Soares-Miranda L, Sattelmair J, Chaves P, Duncan GE, Siscovick DS, Stein PK, Mozaffarian D. Physical activity and heart rate variability in older adults: The cardiovascular health study. *Circulation* 129: 2100-2110, 2014.
264. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, Macchi C. Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *J Intern Med* 269: 107-117, 2011.
265. Sorbini C, Grassi V, Solinas E, Muisan G. Arterial oxygen tension in relation to age in healthy subjects. *Respiration* 25: 3-13, 1968.
266. Sousa AS, Guerra RS, Fonseca I, Pichel F, Ferreira S, Amaral TF. Financial impact of sarcopenia on hospitalization costs. *Eur J Clin Nutr* 70: 1046-1051, 2016.
267. Spahillari A, Mukamal K, Defilippi C, Gottdiener JS, Djoussé L, Lyles MF, Bartz TM, Murthy VL, Shah RV. The association of lean and fat mass with all-cause mortality in older adults: the cardiovascular health study. *Nutr Metab Cardiovasc Dis* 26: 1039-1047, 2016.
268. Spina RJ, Turner MJ, Ehsani AA. Beta-adrenergic-mediated improvement in left ventricular function by exercise training in older men [Online]. *Am J Physiol* 274: H397-H404, 1998. http://www.ncbi.nlm.nih.gov/pubmed/9486240
269. Steffl M, Sima J, Shiells K, Holmerova I. The increase in health care costs associated with muscle weakness in older people without long-term illnesses in the Czech Republic: results from the survey of health, ageing and retirement in Europe (SHARE). *Clin Interv Aging* 12: 2003-2007, 2017.
270. Straight CR, Lindheimer JB, Brady AO, Dishman RK, Evans EM. Effects of resistance training on lower-extremity muscle power in middle-aged and older adults: A systematic review and meta-analysis of randomized controlled trials. *Sports Med* 46: 353-364, 2016.
271. Stratton JR, Cerqueira MD, Schwartz RS, Levy WC, Veith RC, Kahn SE, Abrass IB. Differences in cardiovascular responses to isoproterenol in relation to age and exercise training in healthy men. *Circulation* 86: 504-512, 1992.
272. Studenski S. Gait speed and survival in older adults. *JAMA* 305: 50, 2011.
273. Subra J, Gillette-Guyonnet S, Cesari M, Oustric S, VellaS B. The integration of frailty into clinical practice: Preliminary results from the gérontopôle. *J Nutr Health Aging* 16: 714-720, 2012.
274. Suetta C, Frandsen U, Mackey AL, Jensen L, Hvid LG, Bayer ML, Petersson SJ, Schrøder HD, Andersen JL, Aagaard P, Schjerling P, Kjaer M. Ageing is associated with diminished muscle re-growth and myogenic precursor cell expansion early after immobility-induced atrophy in human skeletal muscle. *J Physiol* 591: 3789-3804, 2013.
275. Sun N, Youle R, Finkel T. The mitochondrial basis of aging. *Mol Cell* 61: 654-666, 2016.
276. Takano H, Morita T, Iida H, Asada KI, Kato M, Uno K, Hirose K, Matsumoto A, Takenaka K, Hirata Y, Eto F, Nagai R, Sato Y, Nakajima T. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. *Eur J Appl Physiol* 95: 65-73, 2005.
277. Tanner RE, Brunker LB, Agergaard J, Barrows KM, Briggs RA, Kwon OS, Young LM, Hopkins PN, Volpi E, Marcus RL, Lastayo PC, Drummond MJ. Age-related differences in lean mass, protein synthesis and skeletal muscle markers of proteolysis after bed rest and exercise rehabilitation. *J Physiol* 593: 4259-4273, 2015.
278. Thom JM, Morse CI, Birch KM, Narici MV. Influence of muscle architecture on the torque and power-velocity characteristics of young and elderly men. *Eur J Appl Physiol* 100: 613-619, 2007.
279. Thomas AW, Davies NA, Moir H, Watkeys L, Ruffino JS, Isa SA, Butcher LR, Hughes MG, Morris K, Webb R. Exercise-associated generation of PPAR ligands activates PPAR signaling events and upregulates genes related to lipid metabolism. *J Appl Physiol* 112: 806-815, 2012.
280. Thurlbeck W, Angus G. Growth and aging of the normal human lung. *Chest* 67: 3S-7S, 1975.
281. Ticinesi A, Meschi T, Narici MV, Lauretani F, Maggio M. Muscle ultrasound and sarcopenia in older individuals: A clinical perspective. *J Am Med Dir Assoc* 18: 290-300, 2017.
282. Tosato M, Marzetti E, Cesari M, Savera G, Miller RR, Bernabei R, Landi F, Calvani R. Measurement of muscle mass in sarcopenia: From imaging to biochemical markers. *Aging Clin Exp Res* 29: 19-27, 2017.
283. Tschopp M, Sattelmayer MK, Hilfiker R. Is power training or conventional resistance training better for function in elderly persons? A meta-analysis. *Age Ageing* 40: 549-556, 2011.
284. Valenzuela PL, Morales JS, Pareja-Galeano H, Izquierdo M, Emanuele E, de la Villa P, Lucia A. Physical strategies to prevent disuse-induced functional decline in the elderly. *Ageing Res Rev* 47: 80-88, 2018.

285. Vasunilashorn S, Coppin AK, Patel KV, Lauretani F, Ferrucci L, Bandinelli S, Guralnik JM. Use of the short physical performance battery score to predict loss of ability to walk 400 meters: Analysis from the InCHIANTI study. *Journals Gerontol—Ser A Biol Sci Med Sci* 64: 223-229, 2009.
286. Vechin F, Libardi C, Conceiao M, Damas F, Lixandrao M, Berton R, Tricoli V, Roschel H, Cavaglieri C, Chacon-Mikahil M, Ugrinowitsch C. Comparisons between low-intensity resistance training with blood flow restriction and high-intensity resistance training on quadriceps muscle mass and strength in elderly. *J Strength Cond Res* 29: 1071-1076, 2015.
287. Velloso CP. Regulation of muscle mass by growth hormone and IGF-I. *BrJPharmacol* 154: 557-568, 2008.
288. Vigelsø A, Gram M, Wiuff C, Andersen JL, Helge JW, Dela F. Six weeks' aerobic retraining after two weeks' immobilization restores leg lean mass and aerobic capacity but does not fully rehabilitate leg strength in young and older men. *J Rehabil Med* 47: 552-560, 2015.
289. Vinstrup J, Skals S, Calatayud J, Jakobsen MD, Sundstrup E, Pinto MD, Izquierdo M, Wang Y, Zebis MK, Andersen LL. Electromyographic evaluation of high-intensity elastic resistance exercises for lower extremity muscles during bed rest. *Eur J Appl Physiol* 117: 1329-1338, 2017.
290. Visser M, Fuerst T, Lang T, Salamone L, Harris TB, Health FT, Absorptiometry ACSD-E, Group BCW. Validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass. *J Appl Physiol* 87: 1513-1520, 1999.
291. Volpato S, Cavalieri M, Sioulis F, Guerra G, Maraldi C, Zuliani G, Fellin R, Guralnik JM. Predictive value of the short physical performance battery following hospitalization in older patients. *J Gerontol – Ser A Biol Sci Med Sci* 66 A: 89-96, 2011.
292. Volpi E, Sheffield-Moore M, Rasmussen B, Wolfe R. Basal muscle amino acid kinetics and protein synthesis in healthy young and older men. *JAMA* 286: 1206-1212, 2001.
293. de Vries NM, van Ravensberg CD, Hobbelen JSM, Olde Rikkert MGM, Staal JB, Nijhuis-van der Sanden MWG. Effects of physical exercise therapy on mobility, physical functioning, physical activity and quality of life in community-dwelling older adults with impaired mobility, physical disability and/or multi-morbidity: A meta-analysis. *Ageing Res Rev* 11: 136-149, 2012.
294. Wall BT, Snijders T, Senden JMG, Ottenbros CLP, Gijsen AP, Verdijk LB, Van Loon LJC. Disuse impairs the muscle protein synthetic response to protein ingestion in healthy men. *J Clin Endocrinol Metab* 98: 4872-4881, 2013.
295. Watanabe K, Holobar A, Kouzaki M, Ogawa M, Akima H, Moritani T. Age-related changes in motor unit firing pattern of vastus lateralis muscle during low-moderate contraction. *Age (Omaha)* 38, 2016.
296. Watenpaugh DE, Ballard RE, Schneider SM, Lee SM, Ertl AC, William JM, Boda WL, Hutchinson KJ, Hargens AR. Supine lower body negative pressure exercise during bed rest maintains upright exercise capacity. *J Appl Physiol* 89: 218-227, 2000.
297. Wernbom M, Apro W, Paulsen G, Nilsen TS, Blomstrand E, Raastad T. Acute low-load resistance exercise with and without blood flow restriction increased protein signalling and number of satellite cells in human skeletal muscle. *Eur J Appl Physiol* 113: 2953-2965, 2013.
298. Wilkes E, Selby A, Atherton P, Patel R, Rankin D, Smith K, Rennie M. Blunting of insulin inhibition of proteolysis in legs of older subjects may contribute to age-related sarcopenia. *Am J Clin Nutr* 90: 1343-1350, 2009.
299. Wilkinson DJ, Piasecki M, Atherton PJ. The age-related loss of skeletal muscle mass and function: Measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. *Ageing Res Rev* 47: 123-132, 2018.
300. Yasuda T, Fukumura K, Fukuda T, Uchida Y, Iida H, Meguro M, Sato Y, Yamasoba T, Nakajima T. Muscle size and arterial stiffness after blood flow-restricted low-intensity resistance training in older adults. *Scand J Med Sci Sport* 24: 799-806, 2014.
301. Yazdanyar A, Newman A. The burden of cardiovascular disease in the elderly: Morbidity, mortality, and costs. *Clin Geriatr Med* 25: 563-567, 2009.
302. Yoshiko A, Hioki M, Kanehira N, Shimaoka K, Koike T, Sakakibara H, Oshida Y, Akima H. Three-dimensional comparison of intramuscular fat content between young and old adults. *BMC Med Imaging* 17: 1-8, 2017.
303. Yuki A, Ando F, Otsuka R, Shimokata H. Low free testosterone is associated with loss of appendicular muscle mass in Japanese community-dwelling women. *Geriatr Gerontol Int* 15: 326-333, 2015.
304. Yuki A, Otsuka R, Kozakai R, Kitamura I, Okura T, Ando F, Shimokata H. Relationship between low free testosterone levels and loss of muscle mass. *Sci Rep* 3: 1-5, 2013.
305. Zanchi NE, Lancha AH. Mechanical stimuli of skeletal muscle: Implications on mTOR/p70s6k and protein synthesis. *Eur J Appl Physiol* 102: 253-263, 2008.
306. Zheng SX, Vrindts Y, Lopez M, De Groote D, Zangerle PF, Collette J, Franchimont N, Geenen V, Albert A, Reginster JY. Increase in cytokine production (IL-1β, IL-6, TNF-α but not IFN-γ, GM-CSF or LIF) by stimulated whole blood cells in postmenopausal osteoporosis. *Maturitas* 26: 63-71, 1997.
307. Zisberg A, Shadmi E, Gur-Yaish N, Tonkikh O, Sinoff G. Hospital-associated functional decline: The role of hospitalization processes beyond individual risk factors. *J Am Geriatr Soc* 63: 55-62, 2015.
308. Zisberg A, Shadmi E, Sinoff G, Gur-Yaish N, Srulovici E, Admi H. Low mobility during hospitalization and functional decline in older adults. *J Am Geriatr Soc* 59: 266-273, 2011.

Effects of lifelong exercise on aging-induced physical fitness decline

In order to assess the effect of lifelong exercise on aging-induced functional decline, we compiled evidence on the VO_{2max} values reported in athletes across different ages (from young up to centenarian athletes) compared to the age-matched general population. We also reviewed the main physiological mechanisms underlying lifelong endurance exercise benefits on age-related VO_{2max} decline. We show that VO_{2max} decreases with aging, but lifelong physical exercise exerts a myriad of benefits (i.e., enhanced or at least preserved levels of pulmonary/cardiovascular function, blood oxygen carrying capacity, skeletal muscle capillary density and oxidative capacity) which in turn seem to attenuate the rate of aging-related VO_{2max} decline. This narrative review was published in Sports Medicine (impact factor: 7.583, position: 2/83, category: Sports medicine),[53] and a representative scheme is available as Figure 2.

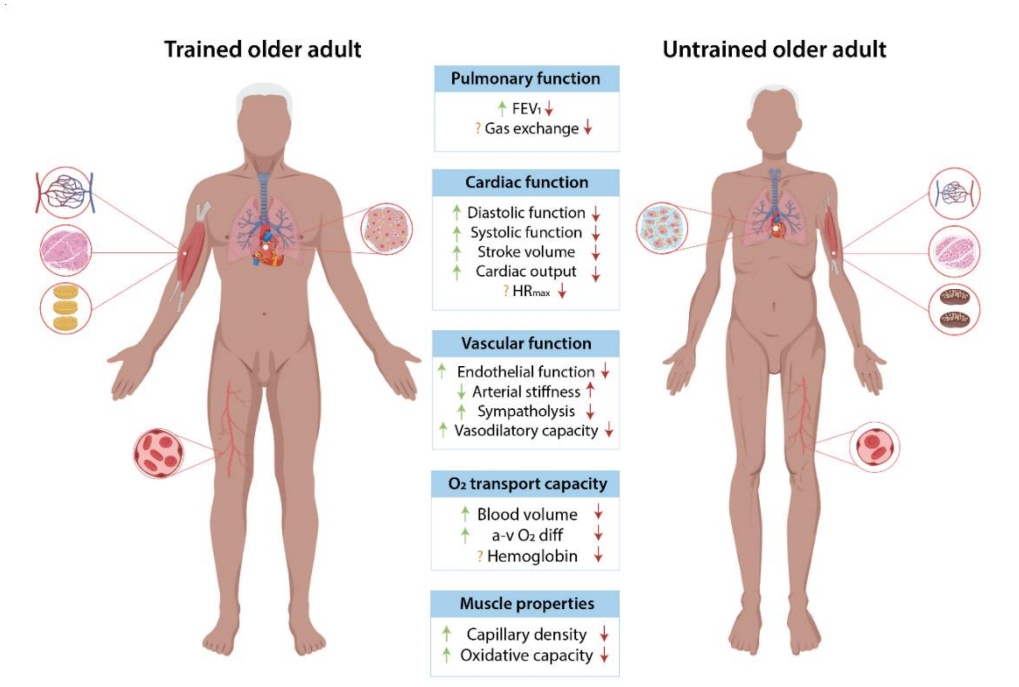


Figure 2. Summary of the physiological benefits of lifelong endurance exercise for the prevention of aging-induced decline in physical fitness (maximum oxygen uptake).

Sports Medicine
https://doi.org/10.1007/s40279-019-01252-0

REVIEW ARTICLE

Lifelong Endurance Exercise as a Countermeasure Against Age-Related $\dot{V}O_{2max}$ Decline: Physiological Overview and Insights from Masters Athletes

Pedro L. Valenzuela[1,2] · Nicola A. Maffiuletti[3] · Michael J. Joyner[4] · Alejandro Lucia[5,6] · Romuald Lepers[7]

Abstract

Maximum oxygen consumption ($\dot{V}O_{2max}$) is not only an indicator of endurance performance, but also a strong predictor of cardiovascular disease and mortality. This physiological parameter is known to decrease with aging. In turn, physical exercise might attenuate the rate of aging-related decline in $\dot{V}O_{2max}$, which in light of the global population aging is of major clinical relevance, especially at advanced ages. In this narrative review, we summarize the evidence available from masters athletes about the role of lifelong endurance exercise on aging-related $\dot{V}O_{2max}$ decline, with examples of the highest $\dot{V}O_{2max}$ values reported in the scientific literature for athletes across different ages (e.g., 35 ml·kg^{-1}·min^{-1} in a centenarian cyclist). These data suggest that a linear decrease in $\dot{V}O_{2max}$ might be possible if physical exercise loads are kept consistently high through the entire life span, with $\dot{V}O_{2max}$ values remaining higher than those of the general population across all ages. We also summarize the main physiological changes that occur with inactive aging at different system levels—pulmonary and cardiovascular function, blood O_2 carrying capacity, skeletal muscle capillary density and oxidative capacity—and negatively influence $\dot{V}O_{2max}$, and review how lifelong exercise can attenuate or even prevent most—but apparently not all (e.g., maximum heart rate decline)—of them. In summary, although aging seems to be invariably associated with a progressive decline in $\dot{V}O_{2max}$, maintaining high levels of physical exercise along the life span slows the multi-systemic deterioration that is commonly observed in inactive individuals, thereby attenuating age-related $\dot{V}O_{2max}$ decline.

Key Points

Masters athletes are considered a paradigm of healthy aging because they are able to maintain high levels of exercise at advanced ages and show remarkable physical/physiological function compared to their inactive peers.

Maximum oxygen consumption ($\dot{V}O_{2max}$) decreases with aging, but lifelong physical exercise exerts a myriad of benefits (i.e., enhanced or at least preserved levels of pulmonary/cardiovascular function, blood O_2 carrying capacity, skeletal muscle capillary density and oxidative capacity) which in turn seem to attenuate the rate of aging-related $\dot{V}O_{2max}$ decline.

Given the role of $\dot{V}O_{2max}$ as a strong predictor of cardiovascular disease and mortality, these findings support the need to perform high levels of physical exercise across all ages.

✉ Pedro L. Valenzuela
pedrol.valenzuela@edu.uah.es

1 Physiology Unit, Department of Systems Biology, School of Medicine, University of Alcalá, Ctra. Barcelona, Km 33,600, 28871 Alcalá De Henares, Madrid, Spain

2 Department of Sport and Health, Spanish Agency for Health Protection in Sport (AEPSAD), Madrid, Spain

3 Human Performance Lab, Schulthess Klinik, Zurich, Switzerland

4 Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, USA

5 Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain

6 Instituto de Investigación Sanitaria Hospital 12 de Octubre ('i+12'), CIBERFES, Madrid, Spain

7 INSERM UMR1093, Cognition Action et Plasticité Sensorimotrice, University of Bourgogne Franche-Comté, Dijon, France

Published online: 24 December 2019

1 Introduction

Maximum oxygen consumption ($\dot{V}O_{2max}$), that is, the maximum integrative ability of the organism to transfer oxygen (O_2) from the atmosphere to be utilized by the mitochondria of working muscles [1], is widely considered the gold standard measurement of cardiorespiratory fitness [2]. $\dot{V}O_{2max}$ is well known to decrease with aging [3], and the rate of decline further accelerates at advanced ages [4]. Besides being a main limiting factor of endurance performance [1], $\dot{V}O_{2max}$ is a strong cardiovascular and all-cause mortality predictor [5–7]. Moreover, the exponential decline of physical fitness—including $\dot{V}O_{2max}$—that occurs with aging is a major contributor to loss of functionality and frailty [8], with the latter condition affecting one to two of every four individuals aged ≥ 85 years and thus being considered a major health problem [9]. Thus, attenuation of aging-related $\dot{V}O_{2max}$ decline is of clinical relevance.

The age-related decrease in physical/physiological function is currently exacerbated by the growing epidemic of inactivity, with at least one of every four individuals performing less than the minimum WHO-recommended amount of physical activity (PA) (≥ 150 min per week of moderate–vigorous PA, such as walking/brisk walking) [10]. Maintaining high levels of PA through the life span seems to be a necessary condition to attenuate the age- and inactivity-related decline in physiological function [11, 12]. Regular endurance exercise (e.g., running) is probably the most effective strategy for enhancing or preserving $\dot{V}O_{2max}$ levels over time, and there is evidence that this strategy can be beneficial even at the most advanced ages [13]. In this regard, masters endurance athletes (i.e., individuals > 40 years old who still actively participate in sports competitions) have been proposed as a paradigm of healthy aging because most are able to maintain high levels of endurance exercise and show a remarkable physical and physiological function compared to their sedentary peers [14–16].

In this narrative review, we summarize the evidence available on the impact of lifelong endurance exercise as a countermeasure against age-related $\dot{V}O_{2max}$ decline, supporting these benefits with cross-sectional data of the highest $\dot{V}O_{2max}$ values reported in athletes across different ages compared to the age-matched general population. We also review the main physiological mechanisms underlying lifelong endurance exercise benefits on age-related $\dot{V}O_{2max}$ decline.

2 Lifelong Endurance Exercise as a Countermeasure Against $\dot{V}O_{2max}$ Decline: Epidemiological Evidence in Masters Athletes

There are data supporting that endurance exercise levels might modulate the relationship between aging and $\dot{V}O_{2max}$ [17]. A classic study by Dehn and Bruce [18] reported that trained individuals present with an attenuated age-related decline in $\dot{V}O_{2max}$ compared to their untrained peers. There is, however, controversy on this topic, with meta-analytical evidence showing either no differences in $\dot{V}O_{2max}$ decline between endurance-trained and inactive men [19], or even a greater decline in the former [20]. Other studies reported that, although endurance-trained older adults had a higher absolute ($l \cdot min^{-1}$) and relative $\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) than their inactive peers at any age, the rate of $\dot{V}O_{2max}$ decline with aging (expressed in $ml \cdot kg^{-1} \cdot min^{-1} \cdot year^{-1}$, but not as a %) was also greater in the former [21, 22]. However, inactive individuals presented with a progressive reduction in VO_{2max} across all ages, whereas endurance-trained athletes did not show this decline until a more advanced age (~ 50 years) [22].

The relative reduction in PA levels with aging is greater in trained than in untrained individuals, and this has been proposed as one of the main factors underlying the differences in the rate of $\dot{V}O_{2max}$ decline [14]. Several studies have proposed that the decrease in $\dot{V}O_{2max}$ with aging is modulated by age-related decreases in training levels [21–24]. For instance, in a longitudinal study of individuals aged ~ 64 years, Katzel et al. [24] observed that those participants who stopped training during the following ~ 9 years lost on average 4.6% of $\dot{V}O_{2max}$ per year, whereas those who maintained high levels of exercise during this period only lost 0.3% per year. These findings are in line with classical longitudinal studies reporting a greater $\dot{V}O_{2max}$ decline in inactive older adults compared to masters endurance athletes who had maintained their training levels during a follow-up period [25, 26]. Thus, although performing physical exercise during youth and adulthood might help to reach older ages with a remarkable $\dot{V}O_{2max}$ level compared to sedentary individuals, keeping exercise levels high later in life—including at the most advanced ages—seems to be a necessary condition to attenuate the usual age-related $\dot{V}O_{2max}$ decline.

Confirming the benefits of exercise on $\dot{V}O_{2max}$ at advanced ages, a recent study reported that individuals aged ~ 72 to 74 years who had exercised regularly (~ 5 days/week) over the past ~ 52 years had a 44% higher $\dot{V}O_{2max}$ than their inactive peers [27]. Trappe et al. [28] showed that even at the most advanced ages (> 80 years) lifelong exercisers (> 50 years of endurance exercise) presented with a markedly higher $\dot{V}O_{2max}$ than their inactive counterparts (~ 38

vs ~21 ml·kg^{-1}·min^{-1}, respectively). The research group of Levine and co-workers has also consistently demonstrated that older adults (> 65 years) who maintain high levels of endurance exercise during 20–25 years or more attenuate or even prevent the age-related $\dot{V}O_{2max}$ decline compared to those who remain inactive during an equivalent time period [29–33]. Meta-analytical evidence has confirmed that masters athletes (mean age > 55 years) have higher $\dot{V}O_{2max}$ values than their inactive counterparts and similar values to those of untrained healthy young controls [34, 35]. In this regard, there seems to be a dose–response relationship between the levels of lifelong physical exercise (i.e., in terms of intensity, volume, or frequency [number of weekly sessions] of training) and the benefits on $\dot{V}O_{2max}$. Carrick-Ranson et al. [32] and Hieda et al. [33] found that those individuals (mean age 68–71 years) who performed physical exercise more frequently during the past 25 years (≥ 4 to 5 sessions per week) had the highest $\dot{V}O_{2max}$ values, whereas no differences in $\dot{V}O_{2max}$ were found between inactive individuals and those who performed 2 to 3 sessions of exercise per week. Thus, increasing training levels by manipulating either training frequency or particularly training volume (distance or time completed in each session) and/or intensity (e.g., watts, speed) might be factors modulating the benefits of lifelong exercise on VO_{2max} [36, 37].

3 VO_{2max} Records in Masters Athletes

Masters athletes of different ages present with a higher $\dot{V}O_{2max}$ than age-matched inactive individuals, which supports the beneficial role of lifelong physical exercise to attenuate the age-related VO_{2max} decline at advanced ages, particularly if physical training levels are kept consistently high. As shown in Fig. 1, which displays the highest $\dot{V}O_{2max}$ values found in the scientific literature for athletes of different ages, lifelong endurance exercise can result in $\dot{V}O_{2max}$ values 20–40% higher than the 95th percentile of the age-reference values provided by the American College of Sports Medicine [38]. Levels of $\dot{V}O_{2max}$ > 90 ml·kg^{-1}·min^{-1} have been reported for some young male elite athletes [39, 40], who probably present with the highest $\dot{V}O_{2max}$ values ever reported. In turn, $\dot{V}O_{2max}$ levels well above the average reference values for younger healthy individuals [38] have been reported for runners aged 47–62 years (63–76 ml·kg^{-1}·min^{-1}) [41–43] and markedly high $\dot{V}O_{2max}$ levels can still be present in older adults, as reflected by several studies reporting values between 50 and 59 ml·kg^{-1}·min^{-1} for individuals aged 70–80 years [41, 42, 44, 45]. Of note, a remarkably high $\dot{V}O_{2max}$ value of 42.3 ml·kg^{-1}·min^{-1} has been recently reported in an 83-year old female masters athlete, the highest value ever recorded for women older than 80 years

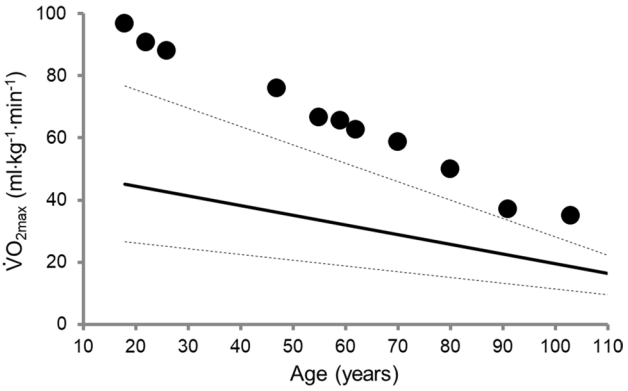


Fig. 1 Highest maximum oxygen consumption ($\dot{V}O_{2max}$) values reported in the scientific literature for athletes of different ages (black circles). The solid line represents the 50th percentile of $\dot{V}O_{2max}$ according to the normative values provided by the American College of Sports Medicine [38], and the dotted lines represent the 5th and 95th percentiles. As reference values were only available up to the age of 65–75 years, reference values from that age were estimated through linear extrapolation. $\dot{V}O_{2max}$ individual data were obtained from the following references [28, 39–45, 47, 136]

[46]. Moreover, $\dot{V}O_{2max}$ values of 37 ml·kg^{-1}·min^{-1} and 35 ml·kg^{-1}·min^{-1}, which correspond to the expected value for individuals aged 35–45 years [38], have been reported during cycle-ergometer testing in endurance athletes aged 91 and 103 years, respectively [28, 47].

It is traditionally believed that an exponential decline in physical/physiological function occurs with aging, particularly after 70–80 years of age (known as 'break point') [15]. For instance, longitudinal data from the masters athlete Ed Whitlock (first person > 70 years old to run a sub 3-h marathon) suggests that despite having an estimated VO_{2max} value of ~ 50 ml·kg^{-1}·min^{-1} at 80 years, he showed an accelerated decline in running performance after age 80 (he died at age 86 from prostate cancer) [48]. However, the values presented in Fig. 1 suggest that a linear decline in $\dot{V}O_{2max}$ with aging is theoretically possible even at the most advanced ages (e.g., 100 years). Indeed, when trying to fit these $\dot{V}O_{2max}$ values to an exponential and a linear function, the resulting fit is worse for the former ($R^2 = 0.96$ vs 0.99, respectively). The possible existence of a linear decline in $\dot{V}O_{2max}$ with aging has also been inferred by the authors of a cross-sectional study performed in highly active individuals (cyclists) aged up to 79 years [49]. Interestingly, if our data were fitted with an exponential equation the results would suggest a greater decline at younger ages than at advanced ones, which is in contrast to what is traditionally thought [15]. In this line, cross-sectional $\dot{V}O_{2max}$ values from more than 4000 individuals aged between 20 and 79 years showed a $\dot{V}O_{2max}$ decline of 10% per decade [50], which would result in an

exponential decline in this parameter when expressed in absolute values ($l \cdot min^{-1}$). Further research is, however, needed to confirm if the aforementioned rate of decline is observed in later years of life (i.e., above age 80). The trend observed in $\dot{V}O_{2max}$ records reported here also suggests a faster decline in masters athletes than in the general population (at least when compared with normative values). It remains to be elucidated whether an eventual faster aging-related $\dot{V}O_{2max}$ decline in masters athletes compared to inactive people is caused by greater relative reductions in exercise levels over time in the former—as some longitudinal studies have proposed [21, 23, 24] —or alternatively, to a greater relative physiological deterioration independent of training status.

It must be noted that our analysis has some limitations, as it is cross-sectional, based on a thorough but not systematic search, and does not take into account several potential confounding factors (e.g., socio-economic status, or presence of diseases that aggravate physiological decline). Although $\dot{V}O_{2max}$ levels might show a theoretical linear decline with aging, there is no evidence from longitudinal studies to support that the occurrence of an age-related 'break point' in $\dot{V}O_{2max}$ can be actually prevented with regular exercise, particularly at the most advanced ages. Moreover, the paucity of longitudinal studies hinders drawing solid conclusions on how does lifelong exercise actually modulate the inherent age-related decline in $\dot{V}O_{2max}$. In this regard, it may be hypothesized that masters athletes already had high $\dot{V}O_{2max}$ values at baseline (i.e., before engaging in training), or that they have a higher responsiveness or lower sensitivity to training and inactivity, respectively, compared to the general population. In this context, a recent case study showed that a 59-year-old world record marathon holder for his age group (and former Olympic-class runner) had retained a very high $\dot{V}O_{2max}$ value, 65.4 $ml \cdot kg^{-1} \cdot min^{-1}$—which is in fact, the highest known for his age—despite a 16-year break in training after he retired from competition at 32 years old [43]. It has been however reported that keeping exercise levels high is overall necessary to reduce the rate of age-related $\dot{V}O_{2max}$ decline [21, 23, 24]. Also noteworthy is that, even in the case of a linear decline in $\dot{V}O_{2max}$ with aging, a more abrupt decline might still be found in other variables (e.g., muscle mass or strength) at advanced ages, which would lead to an exponential decline in overall physical performance. Notwithstanding, the present results suggest that the 'break point' in $\dot{V}O_{2max}$ might be, at least partly, delayed if physical exercise loads are kept high across all ages, thereby reducing the risk of having very poor $\dot{V}O_{2max}$ levels at the end of the life span.

Besides the controversial issue of the actual influence of genetics on VO_{2max} trainability [51–53], there are several 'modifiable' physiological mechanisms by which lifelong physical exercise might attenuate the normal age-related $\dot{V}O_{2max}$ decline. As reviewed by Wagner [54], the O_2 pathway from the atmosphere to the mitochondria includes several steps (known as the 'oxygen transport cascade'): convective O_2 transport from air to lung, diffusive O_2 transport from lung to blood, convective O_2 transport in blood from lungs to muscle, and O_2 diffusion from the microcirculation to the tissues and particularly to the mitochondria. In the following section, we will briefly discuss the main physiological systems/factors involved in the different steps of the O_2 transport cascade and thus ultimately influencing $\dot{V}O_{2max}$, how they are affected by the aging process, and the beneficial effects of lifelong exercise (Fig. 2).

4 Physiological Factors Mediating Lifelong Exercise Benefits on $\dot{V}O_{2max}$

4.1 Pulmonary Function

4.1.1 Aging Effects

The convective transport of O_2 from the atmosphere to the lung is mostly mediated by pulmonary function. The latter becomes progressively compromised with aging [55, 56]. An increase in chest wall stiffness together with an impaired strength of ventilatory muscles result in decreased dynamic lung volumes (e.g., as assessed through the forced expiratory volume in one second [FEV_1]) [57]. Aging also results in a progressive decline in the arterial partial pressure of O_2 due to age-induced ventilation-perfusion mismatch [58], with the alveolar surface area decreasing due to alterations in the lung internal geometry [59]. The aforementioned age-induced changes impair maximal ventilatory capacity and pulmonary gas exchange, and thus can also affect $\dot{V}O_{2max}$ [60]. Although pulmonary function is not widely considered a major limiting factor of $\dot{V}O_{2max}$ in healthy young individuals, a compromised pulmonary function seems to be associated, at least partly, with an impaired $\dot{V}O_{2max}$. Some authors have reported a relationship between $\dot{V}O_{2max}$ and pulmonary function—as measured by FEV_1—but just until a given threshold value above which pulmonary function does not seem to limit $\dot{V}O_{2max}$ anymore [61]. It is important to note, however, that the identified threshold values were within the normal limits of lung function for elders, which suggests that pulmonary function might be a limiting factor of $\dot{V}O_{2max}$ in healthy older adults. A recent study reported that FEV_1 values might affect $\dot{V}O_{2max}$ even in healthy young and middle-aged individuals, with both variables being positively associated in subjects with FEV_1 values above the lower limit of normality [62]. Of note, the reason why an aging-related reduction in FEV_1 might partly

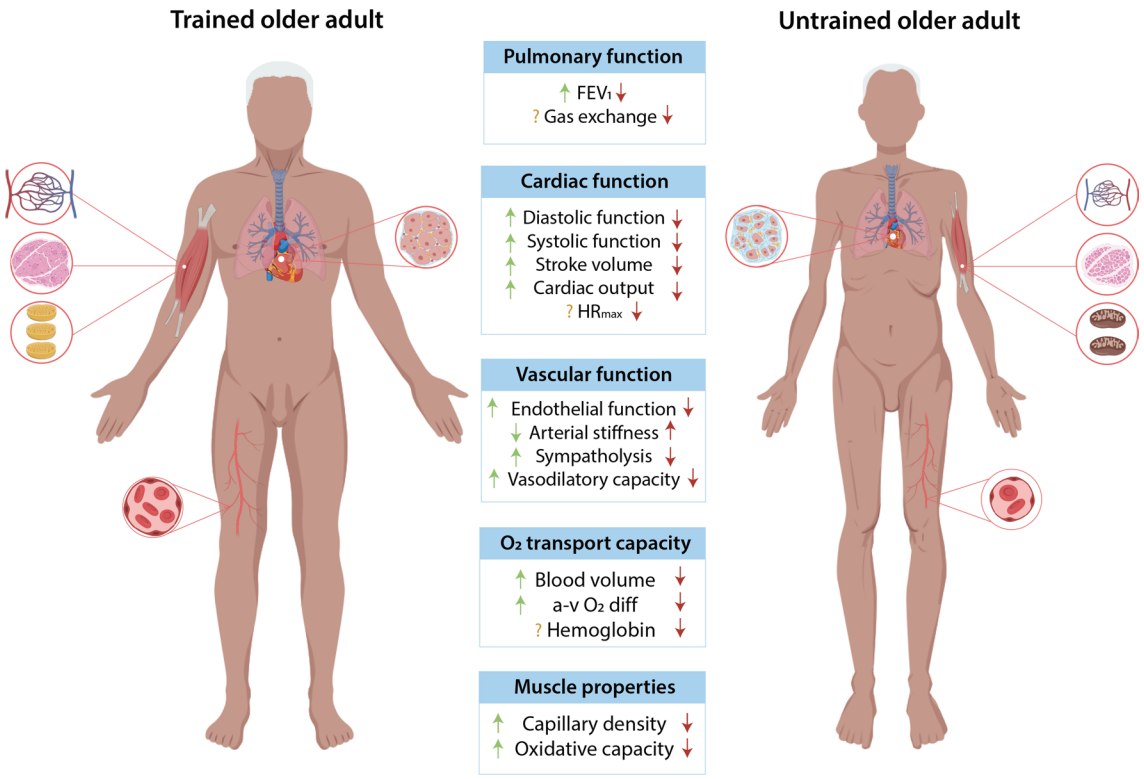


Fig. 2 Effects of aging on the factors affecting maximal oxygen consumption in lifelong exercisers and in untrained individuals. Images in circles represent increased fibrosis at the cardiac level and reduced hemoglobin levels, muscle capillary density and oxidative capacity in untrained individuals, all of which are at least partly attenuated by lifelong endurance exercise. *a-v O_2 diff* arteriovenous oxygen difference, HR_{max} maximum heart rate, FEV_1 forced expiratory volume in 1 s. Arrows indicate increments (↑) or reductions (↓) with lifelong exercise or sedentary behaviors. ? indicates that no consistent benefits of lifelong exercise have been reported

contribute to also reduce $\dot{V}O_{2max}$ values could be that it can reflect mechanical constraints—i.e., the lungs lose elastic recoil, the thorax wall gets stiffer and more restricted—to maximal ventilation capacity during exertion [62]. In turn, because maximal pulmonary ventilation, together with the difference between inspired and expired fractional O_2, is the main factor in the computation of $\dot{V}O_{2max}$ by metabolic carts, even small changes in this variable can affect the final $\dot{V}O_{2max}$ value.

Some studies have used oxygen–helium mixture (HeO_2 or 'heliox') to reduce the resistive load against ventilation during exercise, which could potentially enhance pulmonary function—and thus theoretically improve $\dot{V}O_{2max}$. In sedentary older adults, breathing heliox increased the ventilatory response to maximal exercise and tidal volume compared to breathing room air, and this was accompanied by a slight increase in performance (time to exhaustion) during incremental exercise [63]. The same ventilatory responses have been observed in trained older adults and young individuals, but without performance benefits [64, 65]. It must be noted, however, that none of the aforementioned studies assessed changes in $\dot{V}O_{2max}$ and thus it remains unknown whether reductions in pulmonary resistive loads can eventually improve $\dot{V}O_{2max}$. However, evidence to date overall suggests that pulmonary function might be a limiting factor of $\dot{V}O_{2max}$, at least in those individuals in which the former is compromised.

4.1.2 Training Effects

Although there is scarce evidence on the effectiveness of exercise training interventions to prevent the age-related decline in pulmonary function [66], some studies have shown that high levels of endurance exercise can partly attenuate this decline. A recent study in two monozygotic twins aged 52 years found that, although one of them had performed endurance training for more than 30 years and had a $\dot{V}O_{2max}$ ~30% higher compared to his inactive brother, no differences were found in pulmonary function [67]. However, it can be argued that these individuals were not old enough to show age-related deteriorations in pulmonary function. Johnson et al. [68] observed that fit older adults aged 63–77 years ($\dot{V}O_{2max}$ of ~44 ml·kg^{-1}·min^{-1} and a training frequency ≥ 2 times per week) presented with values of vital capacity, total lung capacity, and maximal voluntary ventilation that were 110% of those predicted for their age

and height. Yet, a longitudinal study performed in highly active individuals aged 67–73 years found that lifelong exercise training did not prevent the decline in resting lung volumes and FEV_1 that accompany the normal aging process [69]. However, the latter data were not compared with those of a control group of age-matched inactive subjects.

In turn, a cross-sectional association between PA levels and pulmonary function—as measured by FEV_1—has been found in individuals aged 45–74 years [70]. Moreover, higher levels of vigorous PA were associated with a lower annual relative decline in FEV_1 during a subsequent follow-up [70]. Pelkonen et al. [71] observed in individuals aged 40–59 years that those who performed the highest levels of PA during a 25-year follow-up lost less pulmonary function than those who remained less active. More recent research has shown that, although age was inversely associated with pulmonary function in both masters athletes (35–86 years) and age-matched inactive controls, the former had a 9% higher FEV_1 [72]. However, these results were not explained by differences in maximal ventilatory pressure (i.e., ventilatory muscle strength), which suggests that other 'non-muscular' factors might account for the better pulmonary function observed in masters athletes. Thus, maintaining high levels of physical exercise in the long-term appears to overall attenuate—albeit not prevent—the expected age-related decline in pulmonary function, which in turn would have a beneficial effect on $\dot{V}O_{2max}$. In this regard, however, it must be noted that exercise-induced arterial hypoxemia (EIAH), which is overall rare in older adults [73], is quite prevalent among not only elite masters athletes [74] but also older adults with very high cardiorespiratory fitness [69]. Together with other factors (such as aging-induced reduction in capillary blood volume or perfusion heterogeneity), relative alveolar hypoventilation is a potential contributing factor for very fit old individuals [73, 74].

4.1.3 Key Areas Where More Information is Needed

The relationship between pulmonary function and $\dot{V}O_{2max}$ in healthy individuals remains unclear, and future studies should confirm if the reductions observed with aging in the former can negatively influence $\dot{V}O_{2max}$, especially in those in whom pulmonary function deterioration does not reach pathological limits. Assessing the effects of specific ventilatory muscle training—which has been proven to increase inspiratory muscle function in older adults [75] —on EIAH and $\dot{V}O_{2max}$ could shed some light on this topic. Evidence is also still warranted to elucidate the effects of lifelong physical exercise on pulmonary function, particularly at the most advanced ages. In this regard, even centenarian athletes might improve their pulmonary function (maximal ventilation, respiratory frequency and tidal volume) and $\dot{V}O_{2max}$ with proper training [47]. Thus, although previous studies have suggested that some degree of deterioration in pulmonary function is inevitable with aging, future research should assess if factors such as training frequency or intensity can influence the benefits of physical exercise on pulmonary function, with higher training loads potentially preventing pulmonary functional decline.

4.2 Cardiovascular System

4.2.1 Aging Effects

Together with pulmonary function, the cardiovascular system and particularly maximal cardiac output ($\dot{Q}_{max}$) has been traditionally proposed as one of the major limiting factors of $\dot{V}O_{2max}$ [76]. The two factors that determine $\dot{Q}_{max}$ are maximum stroke volume (SV_{max}) and heart rate (HR_{max}), and although some controversy exists, SV_{max} is usually viewed as the main limiting factor of $\dot{V}O_{2max}$, at least in healthy young individuals [77].

Several age-related changes at the cardiovascular level can explain, at least partly, the aging decline in $\dot{V}O_{2max}$ [55, 78]. With regard to cardiac structural changes, aging is associated with increases in left ventricular (LV) wall thickness, which results from an accumulation of interstitial connective tissue and amyloid deposits as well as from myocyte hypertrophy (albeit there is also a progressive loss in their number, particularly in the sinoatrial node) [78]. These changes result in lower LV compliance and end-diastolic filling compared to younger individuals, which in turn reduce SV_{max} [29, 79]. On the other hand, aging is associated with a reduction in HR_{max}, which seems to be the consequence of an impaired β-adrenergic responsiveness and neurodegeneration [80]. Although as mentioned above SV_{max} is usually identified as the main limiting factor of $\dot{V}O_{2max}$ at the heart level, a reduction in HR_{max} could also potentially reduce $\dot{Q}_{max}$ and consequently $\dot{V}O_{2max}$ [3]. Aging is also associated with increases in fibrosis and calcification of the cardiac valves, stiffness of peripheral and central arteries, and the number of sites for lipid deposition at the vascular level, which leads to a reduced laminar blood flow and thus to a lower O_2 supply to other tissues (e.g., contracting muscles) [78, 81]. Moreover, in young individuals the increased sympathetic vasoconstrictor activity that occurs with exercise is counteracted (a phenomenon known as functional 'sympatholysis') to redistribute blood flow to contracting muscles [82]. By contrast, older adults have a reduced vasodilatory capacity and an impaired functional sympatholysis during exercise, which might compromise O_2 supply and reduce $\dot{V}O_{2max}$ [83]. It has been recently reported that the impaired vasodilatory capacity and functional sympatholysis observed in the older people might be due, at least partly, to a reduction in the deformability of red blood cells, which is associated with an impaired release of

ATP—a vasoactive molecule that stimulates vasodilatation—in response to hemoglobin deoxygenation [84].

4.2.2 Training Effects

There is strong evidence that lifelong exercise can attenuate the age-related deterioration of many of the cardiovascular properties that influence $\dot{V}O_{2max}$. Meta-analytical evidence shows that masters athletes (mean age > 55 years) present with $\dot{Q}_{max}$ values that are higher than those of non-athletes of similar age and similar to those of young healthy controls [35]. Some authors have reported that masters athletes aged 68–70 years present with a preserved LV compliance, diastolic function (i.e., myocardial filling and relaxation) and SV compared to age-matched inactive peers, with these variables being similar to those of young healthy controls [29, 30]. Howden et al. [85] recently reported that, although there were no age- or training-related differences in LV ejection fraction, older adults (~68 years) who had performed lifelong endurance exercise showed a preserved LV systolic longitudinal strain (a marker of systolic function) compared to their inactive peers. Interestingly, these differences disappeared when variations in LV end-diastolic volume were taken into account, which suggests that lifelong exercise prevents the normal age-related reduction in LV systolic function by improving LV diastolic filling [85].

Although lifelong endurance exercise is overall beneficial to attenuate the decline in LV compliance and diastolic function, research has demonstrated that there is a dose–response relationship—and a threshold—for these benefits. Bhella et al. [31] observed that those older adults (> 64 years) who had exercised more frequently during the past 25 years (i.e., ≥ 4 to 5 sessions/week) showed a higher LV compliance and distensibility than their inactive peers. Interestingly, no differences in LV compliance and distensibility were found between individuals who had exercised less frequently (≤ 3 sessions per week) and the inactive group, but $\dot{V}O_{2max}$ values rose linearly with increasing exercise frequency [31]. The same research group showed that those who had performed 4–5 sessions/week during the past 25 years—but not those who had exercised ≤ 3 times per week—presented with a more favorable ventricular-arterial coupling (i.e., dynamic Starling mechanism) and a higher LV end-diastolic volume, SV_{max} and $\dot{Q}_{max}$ than those who had remained inactive [32, 33]. Following the same trend, only those subjects who had exercised ≥ 4 times per week showed a higher $\dot{V}O_{2max}$ than their sedentary counterparts [32].

In contrast to its aforementioned benefits on LV compliance, lifelong exercise does not appear to counteract the decline in HR_{max} that typically accompanies the aging process. For instance, Heath et al. [42] suggested that age-related reductions in HR_{max} were the factor mediating the differences in $\dot{V}O_{2max}$ between trained endurance masters athletes and young athletes; indeed, both groups presented with similar values of LV volume and mass (both being larger than in untrained individuals) but an age-related reduction in HR_{max} was observed in the former. Similarly, Hagberg et al. [86] found that although trained masters athletes presented with a preserved SV_{max} compared to young competitive athletes, the $\dot{Q}_{max}$ and thus the $\dot{V}O_{2max}$ of the former were lower due to a reduced HR_{max} (with a reduction rate similar to that of their inactive counterparts). Research in masters athletes has shown that HR_{max} decreases with aging regardless of training volume, although this reduction does not seem to be related to the change in $\dot{V}O_{2max}$ [87]. Carrick-Ranson et al. [32] also observed no differences in HR_{max} between masters athletes who had performed lifelong exercise (> 25 years with 4–5 sessions/week) and inactive individuals. Nybo et al. [88] observed a yearly reduction in HR_{max} of ~ 1 beat·min^{-1} in an Olympic athlete who was followed for 20 years since he was a 19-year-old. However, this reduction in HR_{max} was compensated for by a proportional increase in O_2 pulse (i.e., the ratio of $\dot{V}O_{2max}$ (mL·min^{-1}) to HR_{max} (beats·min^{-1}) which expresses the volume of O_2 ejected from the ventricles with each cardiac beat) at maximal intensities, resulting in a steady $\dot{V}O_{2max}$ and performance level [88]. Thus, exercise does not seem to exert an influence on the HR_{max} decrease that commonly occurs with aging.

On the other hand, lifelong physical exercise can prevent the age-related decline in endothelial function. Some authors have found that trained older adults had an impaired endothelial function compared to their younger counterparts. Proctor et al. [89] observed a lower leg blood flow and vascular conductance during exercise in trained older adults (55–68 years) with ~ 18 years of experience in endurance exercise (~ 6 h per week) compared to young trained individuals. However, the authors did not assess an additional group of inactive older adults. In this regard, several studies have found that although aging is associated with an increased arterial stiffness, those individuals who perform lifelong exercise present with a lower arterial stiffness and a more preserved endothelium flow-mediated dilation compared to their inactive peers, both being markers related to $\dot{V}O_{2max}$ [81, 90]. The aforementioned benefits are supported by meta-analytical evidence that masters athletes present with an increased flow-mediated dilation compared to age-matched controls [91]. Shibata et al. [92] recently reported in individuals aged > 60 years that those who had trained ≥ 4 to 5 sessions/week at high intensities during the last > 25 years—but not those who had trained less—had a lower central arterial stiffness than their inactive counterparts, although lower training doses (2–3 sessions/week) were enough to observe benefits in carotid artery stiffness and central blood pressure [92]. Moreover, Mortensen et al. [83] showed that lifelong endurance exercise (> 5 h of training per week during the last 30 years in individuals aged ~ 66 years) preserved functional

sympatholysis and attenuated the age-related deterioration in endothelial function and vasodilatory capacity, which could result in an improved blood flow and O_2 supply to working muscles. Groot et al. [93] observed that older adults (mean age of 71–72 years) who performed more than either 30 or 60 min/day of moderate-vigorous PA, respectively, had a preserved vasodilatory capacity compared with their sedentary age-matched controls. Moreover, the $\dot{V}O_{2max}$ of both active groups was higher compared not only to their sedentary age-matched peers but also to a group of sedentary young subjects [93]. In line with these benefits on vasodilatory capacity, it has been reported that the bioavailability of nitric oxide is reduced in inactive older adults whereas lifelong exercise prevents this aging-induced change [94]. In summary, lifelong exercise attenuates the degeneration that occurs in inactive people with aging at both cardiac and vascular level, with subsequent benefits in O_2 supply and $\dot{V}O_{2max}$. However, lifelong exercise does not seem to attenuate the normal age-reduction in HR_{max}.

4.2.3 Key Areas Where More Information is Needed

Evidence on the benefits of lifelong endurance training on SV_{max} and vascular health is quite clear, suggesting that it may attenuate or even prevent the deterioration in LV diastolic filling, LV systolic function, and endothelial function provided a sufficient training frequency/load is applied. There is, however, scarce evidence on whether these beneficial effects are also present at advanced ages (e.g., in those aged 80–85 years and above). There is also controversy on the influence of HR_{max} on $\dot{V}O_{2max}$, with some studies in young subjects suggesting that the former is not a limiting factor [95] while others conducted in older individuals suggesting that the age-related reduction in HR_{max} is the main factor mediating the corresponding $\dot{V}O_{2max}$ decline [42, 86]. In this regard, by replicating the protocol of Munch et al. in older adults [95] it could be analyzed whether increasing HR_{max} above physiological values via atrial pacing could help to increase $\dot{V}O_{2max}$, which would shed some light on the actual role of HR_{max} on $\dot{V}O_{2max}$ in this population.

4.3 Blood Characteristics and Oxygen Carrying Capacity

4.3.1 Aging Effects

Convective O_2 transport in blood from lungs to muscles is another major step in the oxygen transport cascade. The ability to carry O_2 to working muscles, which is mostly mediated by the hemoglobin concentration of the blood, plays a major role in $\dot{V}O_{2max}$. Reductions (e.g., in blood donors or anemic patients) or increases (e.g., blood transfusion) in hemoglobin concentration result in an almost proportional change in $\dot{V}O_{2max}$ [96, 97]. Changes in total hemoglobin mass have been suggested to influence $\dot{V}O_{2max}$ through an increase in the O_2 carrying capacity of the blood, but also through the associated rise in blood volume and subsequent increase in $\dot{Q}_{max}$ [97]. On the other hand, aging is inversely associated with hemoglobin levels [98], and indeed there is a high prevalence (> 20%) of anemia among older adults, particularly in the 'oldest old' [99]. Although the causes of anemia are multifactorial, iron deficiency, renal insufficiency, chronic inflammation and drug interactions have been proposed as potential factors for impaired erythropoiesis with aging [99].

4.3.2 Training Effects

Controversy exists regarding the effects of exercise training on blood O_2 carrying capacity, and the evidence available on its effects in older adults is scarce. However, considering the existing evidence in healthy younger adults, physical exercise might also improve O_2 carrying capacity at advanced ages. Exercise training interventions have been reported to stimulate erythropoiesis, reticulocytosis and blood volume expansion in young individuals—mainly because of an increased plasma volume—and although hemoglobin concentration decreases during training due to hemodilution, total hemoglobin mass increases [100]. Later studies have also reported increases in total hemoglobin mass, red blood cell count and total blood volume with endurance training both at sea level and at altitude in young subjects [101].

On the other hand, it can be hypothesized that lifelong physical exercise might be indirectly beneficial for O_2 supply in older adults by virtue of its protective effects against chronic inflammation and oxidative stress, both of which are prevalent among inactive older adults (a phenomenon known as 'inflammaging') [102] and can negatively affect erythropoiesis [99]. Chronic physical exercise has indeed been proven to attenuate systemic inflammation in older adults, as reflected by decreases in pro-inflammatory markers such as interleukin-6 and C-reactive protein [103]. Although the mechanisms underlying the relationship between inflammation and anemia remain to be elucidated, it has been proposed that excessive levels of inflammation might reduce erythropoietin release, the sensitivity to this hormone, and consequently the proliferation and differentiation of erythroid precursors, also promoting hepcidin synthesis (which reduces iron absorption) and decreasing erythrocyte survival [104, 105].

4.3.3 Key Areas Where More Information is Needed

Although there is biological rationale to support a potential beneficial effect of lifelong endurance training on O_2

carrying capacity, longitudinal studies similar to those analyzing the effects at the cardiovascular level are needed. The documented benefits of endurance exercise training on the hemoglobin mass of young healthy subjects must be corroborated in older people, and particularly in the oldest old, who have an increased risk of anemia [99].

4.4 Muscle Capillary Density and Aerobic Enzyme Activity

4.4.1 Aging Effects

Once in the muscle, the ability to extract O_2 (i.e., diffusive O_2 transport from blood to mitochondria) and to be utilized by mitochondria has been suggested to be the last but essential step for an optimal cardiorespiratory capacity [106]. In this respect, aging is associated with a reduced muscle capillary density [107] as well as with an impaired mitochondrial biogenesis and function [108]. Coley et al. [109] observed that the reduction in muscle oxidative capacity—as reflected by an impaired recovery of muscle creatine phosphate content after exercise—in older adults occurred along with a reduction in the muscle mitochondrial content and oxidative capacity. A reduced local blood flow to contracting muscles was also observed in older adults compared to their younger counterparts, which seems to be partly due to functional impairments in microvascularization [110, 111]. Classical studies reported a relationship between muscle capillary density, mitochondrial density and 'relative' $\dot{V}O_{2max}$ (i.e., expressed relative to body mass, in $ml \cdot kg^{-1} \cdot min^{-1}$) [112, 113], with increases in the latter occurring along with an enhanced capillary density and oxidative enzyme activity [113, 114]. More recently there has been debate on whether the diffusion rate of O_2 from micro-vessels into skeletal muscle is actually a limiting factor of $\dot{V}O_{2max}$ [115, 116]. Gifford et al. [117] suggested that among untrained individuals $\dot{V}O_{2max}$ would be limited by mitochondrial O_2 demand whereas among trained individuals $\dot{V}O_{2max}$ would be limited by O_2 supply despite the presence of a larger mitochondrial respiratory reserve capacity [117]. It has been however recently reported that muscle oxidative capacity was strongly related to relative $\dot{V}O_{2max}$ in individuals with a wide range of $\dot{V}O_{2max}$ values (from 9.8 to 79.0 $ml \cdot kg^{-1} \cdot min^{-1}$), including both trained individuals and patients with chronic heart failure [118]. In the same line, Esposito et al. observed that improvements in muscle capillary density and mitochondrial density lead to an increased $\dot{V}O_{2max}$ in patients with low physical fitness even in the absence of changes in $\dot{Q}max$. [119]. Other authors have found a relationship between muscle oxidative capacity—as assessed through the determination of mitochondrial volume density and citrate synthase activity-, and relative ($ml \cdot kg^{-1} \cdot min^{-1}$) but not 'absolute' ($l \cdot min^{-1}$) $\dot{V}O_{2max}$ [120, 121]. Thus, the delivery of O_2 to skeletal muscle and its utilization by muscle mitochondria should perhaps be viewed as an integrated system, with changes in any step potentially affecting the function of the others [122]. For instance, it has been recently reported that the reductions in $\dot{V}O_{2max}$ observed with aging are associated with a reduction in muscle oxidative capacity, but this association seemed to be mediated by the level of resting muscle perfusion [123]. Layec et al. observed that in sedentary older adults ischemic exercise-induced reactive hyperemia resulted in a greater muscle capillary blood flow and convective O_2 delivery, which led to an improved tissue oxygenation and mitochondrial function [124]. These findings were in line with those reported by Wray et al., who observed that increasing muscle perfusion in elderly subjects through the ingestion of an antioxidant cocktail led to a concomitant increase in muscle oxidative capacity [125]. Of note, no improvements in muscle perfusion or muscle oxidative capacity were observed in young subjects [125]. Thus, impairments in both muscle oxidative capacity and muscle perfusion together with a potential deterioration of previous steps in the O_2 transport cascade seem to play a role in age-related $\dot{V}O_{2max}$ reductions [123]. Particularly, these impairments at the muscle level would result in a reduced arteriovenous O_2 difference (a-vO_2diff) with aging and consequently a lower extraction and utilization of O_2 by the muscle tissue [126, 127].

4.4.2 Training Effects

Endurance exercise has been reported to increase muscle capillary density and oxidative enzymatic activity [114]. Although there are many overlapping pathways involved in these benefits, a key player is the peroxisome proliferator activated receptor γ coactivator 1α (commonly abbreviated as 'PGC-1α'), which promotes mitochondrial biogenesis [128, 129], together with increases in the levels of vascular endothelial growth factor, a signal protein that stimulates angiogenesis [130]. Moreover, lifelong exercise can help to prevent the reduction in muscle capillary density and oxidative capacity that occurs with aging in inactive people. Iversen et al. [131] observed that trained older adults aged 65–75 years who had been engaged in endurance sports for the last 20–50 years had a 40% higher muscle oxidative enzymatic activity and 27% higher muscle capillarization than their untrained counterparts. In line with the aforementioned findings, a recent study [27] showed that older adults aged ~ 72 to 74 years who had performed lifelong exercise (~ 5 days/week during the previous ~ 52 years) had similar levels of muscle capillarization and aerobic enzyme activity in the vastus lateralis to trained individuals aged ~ 25 years (which in turn were 20–90% greater than those of inactive older adults). Other authors also reported a very minor

degree of age-related decline in muscle properties (including mitochondrial protein content) in cyclists aged 55–79 years who had been training for the last ~ 26 years, although a small inverse relationship was found between aging and capillary density in male, but not female, subjects [132]; of note, capillary density was related to training volume in both female and male participants. The benefits of lifelong physical exercise on muscle oxidative capacity seem to be present even at the most advanced ages, as reflected by the 42–54% higher activity of muscle oxidative enzymes found in octogenarian athletes who had performed endurance exercise for > 50 years compared to an age-matched group of inactive individuals [28].

The abovementioned training benefits on muscle capillary density and muscle oxidative capacity would overall result in an attenuated decline of a-vO_2diff with aging. Some studies have indeed reported a higher a-vO_2diff in endurance-trained older adults than in their sedentary counterparts, with the former in fact presenting similar values to those of young individuals [32, 127]. For instance, Carrick-Ranson et al. observed that subjects aged ~ 68 years who had performed endurance exercise regularly during the previous 25 years—and in fact even those doing less than 3 sessions/week—showed a higher a-vO_2diff than those who had remained inactive during an equivalent time period [32]. Thus, lifelong exercise helps to prevent the age-related deterioration in skeletal muscle capillary density and oxidative capacity, which would result in an enhanced extraction and utilization of O_2, and consequently in an improved $\dot{V}O_{2max}$.

4.4.3 Key Areas Where More Information is Needed

Lifelong endurance exercise seems effective to prevent or at least attenuate the age-related decline in muscle capillary density and oxidative capacity. However, as with other factors affecting $\dot{V}O_{2max}$, evidence is lacking on whether these benefits are also present at the most advanced ages. Moreover, despite the potential important role of capillary density and oxidative capacity in $\dot{V}O_{2max}$ as the last step of the oxygen transport cascade, some debate has been raised on the actual influence of these factors [115]. In this respect, a systematic review of 70 studies found that relative increases in $\dot{V}O_{2max}$ with training were overall associated with the changes observed in muscle oxidative capacity [121]. This association, however, was not significant when analyzing older subjects separately, which suggests that there might be other confounding factors (e.g., impairments in previous steps of the O_2 transport cascade) affecting $\dot{V}O_{2max}$ in old people [121].

5 Limitations and Perspectives

The evidence about the benefits of exercise at the most advanced ages (> 80 years) is rather scarce. Although anecdotal data in very old masters athletes would indicate that it is possible to retain a remarkable physical function with proper physical training, these preliminary findings should be confirmed in adequately-powered studies with large cohorts—including also non-athletes in order to assess generalizability to the general population. On the other hand, further research is needed to elucidate the main training-related variables driving exercise benefits on $\dot{V}O_{2max}$. Indeed, most reports refer to training frequency (i.e., days per week) as a modulator of these benefits, but other less studied variables such as training volume or intensity are likely to play a major role. Of note is also the fact that we have consistently used the term $\dot{V}O_{2max}$ throughout our review even though a less valid surrogate, peak oxygen uptake ($\dot{V}O_{2peak}$, that is, the peak value of $\dot{V}O_2$ recorded during maximal exercise testing even when an actual plateau in $\dot{V}O_2$ values or other criteria of maximality were not fulfilled) was the parameter that was actually reported in numerous studies discussed here. Using $\dot{V}O_{2peak}$ might lead to an underestimation of actual $\dot{V}O_{2max}$ values in some individuals, particularly those who are naïve to the test, less motivated, or who are less fit (such as, e.g., patient populations) [133]. Future studies should optimize methodological procedures to ensure an appropriate assessment of VO_{2max}.

Finally, the bulk of scientific evidence in the field comes from studies conducted in men only. Preliminary evidence suggests that oldest old women can also retain high $\dot{V}O_{2max}$ levels with lifelong exercise training [46]. Women usually present with lower values of relative and absolute $\dot{V}O_{2max}$ than men [134], and although they might also show some different physiological adaptations (e.g., lower rates of increase in cardiac mass, SV_{max}, or $\dot{V}O_{2max}$ after one year of endurance training) [135], evidence suggests that the age-related reduction in $\dot{V}O_{2max}$ observed in women is also modulated by reductions in training volume [21]. Research is nevertheless warranted to determine potential between-sex differences in the effects of lifelong exercise on the age-related $\dot{V}O_{2max}$ decline.

6 Conclusions

Although aging has been traditionally associated with an exponential decline in $\dot{V}O_{2max}$ and overall physical function, this association might be confounded by many factors, notably the increasingly inactive lifestyle that often accompanies the aging process in the general population. Although more longitudinal studies are needed, particularly in non-athletes,

current data from masters athletes suggest that the rate of age-related decline in $\dot{V}O_{2max}$ might be modulated by the amount of physical exercise performed over life, with higher levels exerting a marked protective function against the ultimately inevitable aging-induced deterioration in most of the physiological mechanisms that influence $\dot{V}O_{2max}$ (i.e., pulmonary and cardiovascular function, blood oxygen transport capacity, skeletal muscle capillary density and oxidative capacity) (Fig. 2). Future longitudinal studies should, however, confirm this hypothesis as well as the actual role of age-related, non-pathological reductions in some physiological factors (e.g., pulmonary function and HR_{max}) in $\dot{V}O_{2max}$ decline. Overall, given the clinical importance of reaching an advanced age with a preserved functional capacity, the evidence available supports the need for maintaining high levels of physical exercise across all ages, including at an advanced age.

Acknowledgements We sincerely thank Adrián Castillo García (http://www.fissac.com) for designing the figures included in this work.

Compliance with Ethical Standards

Funding The work of Pedro Valenzuela is supported by University of Acalá (FPI2016) and the research by Alejandro Lucia on aging is funded by the Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III (FIS, Grant PI15/00558) and cofunded by 'Fondos FEDER'. No other specific sources of funding were used to assist in the preparation of this article.

Conflict of interest Pedro L. Valenzuela, Nicola A. Maffiuletti, Michael J. Joyner, Alejandro Lucia and Romuald Lepers declare that they have no conflicts of interest relevant to the content of this review.

References

1. Joyner MJ, Coyle EF. Endurance exercise performance: the physiology of champions. J Physiol. 2008;586:35–44.
2. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American heart Association. Circulation. 2016;134:e653–99.
3. Astrand I, Astrand P, Hallback I, Kilbom A. Reduction in maximal oxygen uptake with age. J Appl Physiol. 1973;35:649–54.
4. Fleg J, Morrell C, Bos A, Brant L, Talbot L, Wright J, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults. Circulation. 2005;112:674–82.
5. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood J. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346:793–801.
6. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. JAMA Netw Open. 2018;1:e183605.
7. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events. J Am Med Assoc. 2009;301:2024–35.
8. Lazarus NR, Izquierdo M, Higginson IJ, Harridge SDR. Exercise deiciency diseases of ageing: the primacy of exercise and muscle strengthening as irst line therapeutic agents to combat frailty. J Am Med Dir Assoc. 2018;19:741–3.
9. Clegg A, Young J, Iliffe S, Olde Rikkert M, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752–62.
10. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insuicient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. Lancet Glob. Health. 2018;6:e1077–86.
11. Noakes T, Spedding M. Olympics: run for your life. Nature. 2012;487:295–6.
12. Harridge SDR, Lazarus NR. Physical activity, aging, and physiological function. Physiology. 2017;32:152–61.
13. Valenzuela P, Castillo-García A, Morales J, Izquierdo M, Serra-Rexach J, Santos-Lozano A, et al. Physical exercise in the oldest old. Compr Physiol. 2019;9:1281–304.
14. Tanaka H, Seals DR. Dynamic exercise performance in Masters athletes: insight into the effects of primary human aging on physiological functional capacity. J Appl Physiol. 2003;95:2152–62.
15. Lazarus NR, Harridge SDR. Declining performance of master athletes: silhouettes of the trajectory of healthy human ageing? J Physiol. 2017;595:2941–8.
16. Lepers R, Stapley PJ. Master athletes are extending the limits of human endurance. Front Physiol. 2016;7:1–8.
17. Tanaka H, Seals DR. Endurance exercise performance in Masters athletes: age-associated changes and underlying physiological mechanisms. J Physiol. 2008;586:55–63.
18. Dehn MM, Bruce RA. Longitudinal variations in maximal oxygen intake with age and activity. J Appl Physiol. 1972;33:805–7.
19. Wilson TM, Tanaka H. Meta-analysis of the age-associated decline in maximal aerobic capacity in men: relation to training status. Am J Physiol Circ Physiol. 2000;278:H829–34.
20. Fitzgerald MD, Tanaka H, Tran ZV, Seals DR. Age-related declines in maximal aerobic capacity in regularly exercising vs. sedentary women: a meta-analysis. J Appl Physiol. 1997;83:160–5.
21. Eskurza I, Donato AJ, Moreau KL, Seals DR, Tanaka H. Changes in maximal aerobic capacity with age in endurance-trained women: 7-yr follow-up. J Appl Physiol. 2002;92:2303–8.
22. Pimentel AE, Gentile CL, Tanaka H, Seals DR, Gates PE. Greater rate of decline in maximal aerobic capacity with age in endurance-trained than in sedentary men. J Appl Physiol. 2003;94:2406–13.
23. Trappe SW, Costill DL, Vukovich MD, Jones J, Melham T. Aging among elite distance runners: a 22-yr longitudinal study. J Appl Physiol. 1996;80:285–90.
24. Katzel LI, Sorkin JD, Fleg JL. A comparison of longitudinal changes in aerobic fitness in older endurance athletes and sedentary men. J Am Geriatr Soc. 2001;49:1657–64.
25. Kasch FW, Van Camp S, Nettl F, Wallace JP. Cardiovascular changes with age and exercise: a 28-year longitudinal study. Scand J Med Sci Sports. 1995;5:147–51.
26. Rogers MA, Hagberg JM, Martin WH, Ehsani AA, Holloszy JO. Decline in VO_{2max} with aging in master athletes and sedentary men. J Appl Physiol. 1990;68:2195–9.
27. Gries KJ, Raue U, Perkins RK, Lavin KM, Overstreet BS, D'Acquisto LJ, et al. Cardiovascular and skeletal muscle health with lifelong exercise. J Appl Physiol. 2018;125:1636–45.
28. Trappe S, Hayes E, Galpin A, Jemiolo B, Fink W, Trappe T, et al. New records in aerobic power among octogenarian lifelong endurance athletes. J Appl Physiol. 2013;114:3–10.

29. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, et al. Effect of aging and physical activity on left ventricular compliance. Circulation. 2004;110:1799–805.
30. Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, et al. The effects of aging and physical activity on doppler measures of diastolic function. Am J Cardiol. 2007;99:1629–36.
31. Bhella PS, Hastings JL, Fujimoto N, Shibata S, Carrick-Ranson G, Palmer MD, et al. Impact of lifelong exercise "dose" on left ventricular compliance and distensibility. J Am Coll Cardiol. 2014;64:1257–66.
32. Carrick-Ranson G, Hastings JL, Bhella PS, Fujimoto N, Shibata S, Palmer MD, et al. The effect of lifelong exercise dose on cardiovascular function during exercise. J Appl Physiol. 2014;116:736–45.
33. Hieda M, Howden E, Sarma S, Tarumi T, Palmer D, Lawley J, et al. Impact of lifelong exercise training "dose" on ventricular-arterial coupling. Circulation. 2018;138:2638–47.
34. Mckendry J, Breen L, Shad BJ, Greig CA. Muscle morphology and performance in master athletes: a systematic review and meta-analyses. Ageing Res Rev. 2018;45:62–82.
35. Montero D, Díaz-Cañestro C. Maximal cardiac output in athletes: Influence of age. Eur J Prev Cardiol. 2015;22:1588–600.
36. Bacon AP, Carter RE, Ogle EA, Joyner MJ. VO_{2max} trainability and high Intensity interval training in humans: a meta-analysis. PLoS ONE. 2013;8:e73182.
37. MacInnis MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. J Physiol. 2017;595:2915–30.
38. ACSM. ACSM's guidelines for exercise testing and prescription. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
39. Burtscher M, Nachbauer W, Wilber R. The upper limit of aerobic power in humans. Eur J Appl Physiol. 2011;111:2625–8.
40. Ronnestad BR, Hansen J, Stenlokken L, Joyner M, Lundby C. Case studies in physiology: temporal changes in determinants of aerobic performance in individual going from alpine skier to world champion time trial cyclist. J Appl Physiol. 2019;127:306–11.
41. Everman S, Farris JW, Bay RC, Daniels JT. Elite distance runners: a 45-year follow-up. Med Sci Sports Exerc. 2018;50:73–8.
42. Heath GW, Hagberg JM, Ehsani AA, Holloszy JO. A physiological comparison of young and older endurance athletes. J Appl Physiol. 1981;51:634–40.
43. Lepers R, Bontemps B, Louis J. Physiological profile of a 59-year-old male world record holder marathoner. Med Sci Sports Exerc. 2019. https://doi.org/10.1249/MSS.0000000000002181.
44. Maud PJ, Pollock ML, Foster C, Anholm JD, Guten G, Al-Nouri M, et al. Fifty years of training and competition in the marathon: Wally Hayward, age 70—a physiological profile. S Afr Med J. 1981;59:153–7.
45. Karlsen T, Leinan IM, Bækkerud FH, Lundgren KM, Tari A, Steinshamn SL, et al. How to be 80 year old and have a VO_{2max} of a 35 year old. Case Rep Med. 2015;2015:1–6.
46. Cattagni T, Gremeaux V, Lepers R. The physiological characteristics of an 83-year-old champion female master runner. Int J Sports Physiol Perform. 2019. https://doi.org/10.1123/ijspp.2018-0879.
47. Billat V, Dhonneur G, Mille-Hamard L, Le Moyec L, Momken I, Launay T, et al. Maximal oxygen consumption and performance in a centenarian cyclist. J Appl Physiol. 2017;122:430–4.
48. Lepers R, Cattagni T. Age-related decline in endurance running performance—an example of a multiple World records holder. Appl Physiol Nutr Metab. 2018;43:98–100.
49. Pollock RD, Carter S, Velloso CP, Duggal NA, Lord JM, Lazarus NR, et al. An investigation into the relationship between age and physiological function in highly active older adults. J Physiol. 2015;593:657–80.
50. Kaminsky LA, Imboden MT, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing using cycle ergometry: Data from the Fitness Registry and the importance of Exercise National Database (FRIEND) Registry. Mayo Clin Proc. 2017;92:228–33.
51. Williams CJ, Williams MG, Eynon N, Ashton KJ, Little JP, Wisloff U, et al. Genes to predict VO_{2max} trainability: a systematic review. BMC Genomics. 2017;18:831.
52. Bouchard C. DNA sequence variations contribute to variability in fitness and trainability. Med Sci Sports Exerc. 2019;51:1781–5.
53. Joyner MJ. Limits to the evidence that DNA sequence diferences contribute to the variability in fitness and trainability. Med Sci Sports Exerc. 2019;51:1786–9.
54. Wagner PD. Determinants of maximal oxygen transport and utilization. Annu Rev Physiol. 1996;58:21–50.
55. Aalami O, Fang T, Song H, Nacamuli R. Physiological features of aging persons. Arch Surg. 2003;138:1068–76.
56. Lowery EM, Brubaker AL, Kuhlmann E, Kovacs EJ. The aging lung. Clin Interv Aging. 2013;8:1489–96.
57. Knudson R, Lebowitz M, Holberg C, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis. 1983;127:725–34.
58. Sorbini C, Grassi V, Solinas E, Muisan G. Arterial oxygen tension in relation to age in healthy subjects. Respiration. 1968;25:3–13.
59. Thurlbeck W, Angus G. Growth and aging of the normal human lung. Chest. 1975;67:3S–7S.
60. Bassett D, Howley E. Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc. 2000;32:70–84.
61. Hassel E, Stensvold D, Halvorsen T, Wisløff U, Langhammer A, Steinshamn S. Association between pulmonary function and peak oxygen uptake in elderly: the Generation 100 study. Respir Res. 2015;16:1–8.
62. Rasch-Halvorsen Ø, Steinshamn S, Hassel E, Brumpton BM, Langhammer A. The association between dynamic lung function and peak oxygen uptake in a healthy general population. The HUNT Study. BMC Pulm Med. 2019;19:OA3190.
63. Babb TG. Ventilatory response to exercise in subjects breathing CO_2 or HeO_2. J Appl Physiol. 1997;82:746–54.
64. Babb TG, DeLorey DS, Wyrick BL. Ventilatory response to exercise in aged runners breathing He-O_2 or inspired CO_2. J Appl Physiol. 2003;94:685–93.
65. Babb TG. Ventilation and respiratory mechanics during exercise in younger subjects breathing CO_2 or HeO_2. Respir Physiol. 1997;109:15–28.
66. Roman MA, Rossiter HB, Casaburi R. Exercise, ageing and the lung. Eur Respir J. 2016;48:1471–86.
67. Bathgate KE, Bagley JR, Jo E, Talmadge RJ, Tobias IS, Brown LE, et al. Muscle health and performance in monozygotic twins with 30 years of discordant exercise habits. Eur J Appl Physiol. 2018;118:2097–110.
68. Johnson BD, Reddan WG, Seow KC, Dempsey JA. Mechanical constraints on exercise hyperpnea in a fit aging population. Am Rev Respir Dis. 1991;143:968–77.
69. McClaran SR, Babcock MA, Pegelow DF, Reddan WG, Dempsey JA. Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. J Appl Physiol. 1995;78:1957–68.
70. Jakes RW, Day NE, Patel B, Khaw KT, Oakes S, Luben R, et al. Physical inactivity is associated with lower forced expiratory volume in 1 second: European prospective investigation into

cancer-Norfolk prospective population study. Am J Epidemiol. 2002;156:139–47.
71. Pelkonen M, Notkola IL, Lakka T, Tukiainen HO, Kivinen P, Nissinen A. Delaying decline in pulmonary function with physical activity: a 25-year follow-up. Am J Respir Crit Care Med. 2003;168:494–9.
72. Degens H, Maden-Wilkinson TM, Ireland A, Korhonen MT, Suominen H, Heinonen A, et al. Relationship between ventilatory function and age in master athletes and a sedentary reference population. Age. 2013;35:1007–15.
73. Taylor BJ, Johnson BD. The pulmonary circulation and exercise responses in the elderly. Semin Respir Crit Care Med. 2010;31:528–38.
74. Préfaut C, Anselme F, Caillaud C, Massé-Biron J. Exercise-induced hypoxemia in older athletes. J Appl Physiol. 1994;76:120–6.
75. Mills DE, Johnson MA, Barnett YA, Smith WHT, Sharpe GR. The effects of inspiratory muscle training in older adults. Med Sci Sports Exerc. 2015;47:691–7.
76. Hill A, Lupton H. Muscular exercise, lactic acid, and the supply and utilization of oxygen. Proc R Soc. 1924;97:135–71.
77. Levine BD. VO_{2max}: what do we know, and what do we still need to know? J Physiol. 2008;586:25–34.
78. Lye M, Donnellan C. Heart disease in the elderly. Heart. 2000;84:560–6.
79. Fujimoto N, Hastings JL, Bhella PS, Shibata S, Gandhi NK, Carrick-Ranson G, et al. Effect of ageing on left ventricular compliance and distensibility in healthy sedentary humans. J Physiol. 2012;590:1871–80.
80. Francis Stuart SD, Wang L, Woodard WR, Ng GA, Habecker BA, Ripplinger CM. Age-related changes in cardiac electrophysiology and calcium handling in response to sympathetic nerve stimulation. J Physiol. 2018;596:3977–91.
81. Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation. 1993;88:1456–62.
82. Tschakovsky ME, Sujirattanawimol K, Ruble SB, Valic Z, Joyner MJ. Is sympathetic neural vasoconstriction blunted in the vascular bed of exercising human muscle? J Physiol. 2002;541:623–35.
83. Mortensen SP, Nyberg M, Winding K, Saltin B. Lifelong physical activity preserves functional sympatholysis and purinergic signalling in the ageing human leg. J Physiol. 2012;590:6227–36.
84. Racine M, Dinenno F. Reduced deformability contributes to impaired deoxygenation-induced ATP release from red blood cells of older adult humans. J Physiol. 2019;597:4503–19.
85. Howden EJ, Carrick-Ranson G, Sarma S, Hieda M, Fujimoto N, Levine BD. Effects of sedentary aging and lifelong exercise on left ventricular systolic function. Med Sci Sports Exerc. 2018;50:494–501.
86. Hagberg JM, Allen WK, Seals DR, Hurley BF, Ehsani AA, Holloszy JO. A hemodynamic comparison of young and older endurance athletes during exercise. J Appl Physiol. 1985;58:2041–6.
87. Hawkins SA, Marcell TJ, Jaque SV, et al. A longitudinal VO_{2max} and maximal heart rate in master athletes. Med Sci Sports Exerc. 2001;33:7.
88. Nybo L, Schmidt JF, Fritzdorf S, Nordsborg NB. Physiological characteristics of an aging olympic athlete. Med Sci Sports Exerc. 2014;46:2132–8.
89. Proctor DN, Shen PH, Dietz NM, Eickhoff TJ, Lawler LA, Ebersold EJ, et al. Reduced leg blood flow during dynamic exercise in older endurance-trained men. J Appl Physiol. 1998;85:68–75.
90. Franzoni F, Ghiadoni L, Galetta F, Plantinga Y, Lubrano V, Huang Y, et al. Physical activity, plasma antioxidant capacity, and endothelium-dependent vasodilation in young and older men. Am J Hypertens. 2005;18:510–6.
91. Montero D, Padilla J, Diaz-Cañestro C, Muris DMJ, Pyke KE, Obert P, et al. Flow-mediated dilation in athletes: influence of aging. Med Sci Sports Exerc. 2014;46:2148–58.
92. Shibata S, Fujimoto N, Hastings JL, Carrick-Ranson G, Bhella PS, Hearon CM, et al. The effect of lifelong exercise frequency on arterial stiffness. J Physiol. 2018;596:2783–95.
93. Groot H, Rossman M, Garten R, Wang E, Hoff J, Helgerud J, et al. The effect of physical activity on passive leg movement-induced vasodilation with age. Med Sci Sports Exerc. 2016;48:1548–57.
94. Nyberg M, Blackwell JR, Damsgaard R, Jones AM, Hellsten Y, Mortensen SP. Lifelong physical activity prevents an age-related reduction in arterial and skeletal muscle nitric oxide bioavailability in humans. J Physiol. 2012;590:5361–70.
95. Munch GDW, Svendsen JH, Damsgaard R, Secher NH, González-Alonso J, Mortensen SP. Maximal heart rate does not limit cardiovascular capacity in healthy humans: insight from right atrial pacing during maximal exercise. J Physiol. 2014;592:377–90.
96. Calbet JAL, Lundby C, Koskolou M, Boushel R. Importance of hemoglobin concentration to exercise: acute manipulations. Respir Physiol Neurobiol. 2006;151:132–40.
97. Schmidt WF, Prommer N. Impact of alterations in total hemoglobin mass on VO_{2max}. Exerc Sport Sci Rev. 2010;38:68–75.
98. Salive M, Cornoni-Huntley J, Guralnik J, Philips C, Wallace R, Ostfeld A, et al. Anemia and hemoglobin levels in older persons: relationship with age, gender, and health status. J Am Geriatr Soc. 1992;40:489–96.
99. Steensma DP, Tefferi A. Anemia in the elderly: how should we define it, when does it matter, and what can be done? Mayo Clin Proc. 2007;82:958–66.
100. Schmidt W, Maassen N, Trost F, Böning D. Training induced effects on blood volume, erythrocyte turnover and haemoglobin oxygen binding properties. Eur J Appl Physiol Occup Physiol. 1988;57:490–8.
101. Schmidt W, Heinicke K, Rojas J, Gomez JM, Serrato M, Mora M, et al. Blood volume and hemoglobin mass in endurance athletes from moderate altitude. Med Sci Sports Exerc. 2002;34:1934–40.
102. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Denis Alexander H, Ross OA. Age and age-related diseases: role of inflammation triggers and cytokines. Front Immunol. 2018;9:1–28.
103. Monteiro Junior RS, de Tarso Maciel-Pinheiro P, da Matta M Portugal E, da Silva Figueiredo LF, Terra R, Carneiro LSF, et al. Effect of exercise on inflammatory profile of older persons: systematic review and meta-analyses. J Phys Act Health. 2018;15:65–71.
104. Macciò A, Madeddu C. Management of anemia of inflammation in the elderly. Anemia. 2012;2012:1–20.
105. Nemeth E, Ganz T. Anemia of inflammation. Hematol Oncol Clin N Am. 2014;28:671–81.
106. di Prampero P. Metabolic and circulatory limitations to VO_{2max} at the whole animal level. J Exp Biol. 1985;115:319–31.
107. Groen B, Hamer HM, Snijders T, van Kranenburg J, Frijns D, Vink H, et al. Skeletal muscle capillary density and microvascular function are compromised with aging and type 2 diabetes. J Appl Physiol. 2014;116:998–1005.
108. Chistiakov DA, Sobenin IA, Revin VV, Orekhov AN, Bobryshev YV. Mitochondrial aging and age-related dysfunction of mitochondria. Biomed Res Int. 2014;2014:238463.
109. Conley KE, Jubrias SA, Esselman PC. Oxidative capacity and ageing in human muscle. J Physiol. 2000;526(Pt 1):203–10.
110. Proctor DN, Parker BA. Vasodilation and vascular control in contracting muscle of the aging human. Microcirculation. 2006;13:325–37.
111. Hildebrandt W, Schwarzbach H, Pardun A, Hannemann L, Bogs B, König AM, et al. Age-related differences in skeletal muscle microvascular response to exercise as detected

by contrast-enhanced ultrasound (CEUS). PLoS ONE. 2017;12:1–25.
112. Ingjer F. Maximal aerobic power related to the capillary supply of the quadriceps femoris muscle in man. Acta Physiol Scand. 1978;104:238–40.
113. Hoppeler H, Howald H, Conley K, Lindstedt SL, Claassen H, Vock P, et al. Endurance training in humans: aerobic capacity and structure of skeletal muscle. J Appl Physiol. 1985;59:320–7.
114. Andersen P, Henriksson J. Capillary supply of the quadriceps femoris muscle of man: adaptive response to exercise. J Physiol. 1977;270:677–90.
115. Lundby C, Montero D. CrossTalk opposing view: diffusion limitation of O_2 from microvessels into muscle does not contribute to the limitation of VO_{2max}. J Physiol. 2015;593:3759–61.
116. Wagner PD. CrossTalk proposal: diffusion limitation of O_2 from microvessels into muscle does contribute to the limitation of VO_{2max}. J Physiol. 2015;593:3757–8.
117. Gifford JR, Garten RS, Nelson AD, Trinity JD, Layec G, Witman MAH, et al. Symmorphosis and skeletal muscle VO_{2max}: in vivo and in vitro measures reveal differing constraints in the exercise-trained and untrained human. J Physiol. 2016;594:1741–51.
118. van der Zwaard S, de Ruiter CJ, Noordhof DA, Sterrenburg R, Bloemers FW, de Koning JJ, et al. Maximal oxygen uptake is proportional to muscle fiber oxidative capacity, from chronic heart failure patients to professional cyclists. J Appl Physiol. 2016;121:636–45.
119. Esposito F, Reese V, Shabetai R, Wagner P, Richardson R. Isolated quadriceps training increases maximal exercise capacity in chronic heart failure: the role of skeletal muscle convective and diffusive oxygen transport. J Am Coll Cardiol. 2011;58:1353–62.
120. Lundby C, Jacobs RA. Adaptations of skeletal muscle mitochondria to exercise training. Exp Physiol. 2016;101:17–22.
121. Vigelsø A, Andersen NB, Dela F. The relationship between skeletal muscle mitochondrial citrate synthase activity and whole body oxygen uptake adaptations in response to exercise training. Int J Physiol Pathophysiol Pharmacol. 2014;6:84–101.
122. Wagner PD. Modeling O_2 transport as an integrated system limiting VO_{2max}. Comput Methods Programs Biomed. 2011;101:109–14.
123. Adelnia F, Cameron D, Bergeron C, Fishbein K, Spencer R, Reiter D, et al. The role of perfusion in the age-associated decline of mitochondrial function with aging in healthy individuals. Front Physiol. 2019;10:427.
124. Layec G, Trinity JD, Hart CR, Le Fur Y, Sorensen JR, Jeong EK, et al. Evidence of a metabolic reserve in the skeletal muscle of elderly people. Aging. 2017;9:52–67.
125. Wray DW, Nishiyama SK, Monnet A, Wary C, Duteil SS, Carlier PG, et al. Antioxidants and aging: NMR-based evidence of improved skeletal muscle perfusion and energetics. Am J Physiol Heart Circ Physiol. 2009;297:1870–5.
126. Carrick-Ranson G, Hastings JL, Bhella PS, Shibata S, Fujimoto N, Palmer D, et al. The effect of age-related differences in body size and composition on cardiovascular determinants of VO_{2max}. J Gerontol Ser A Biol Sci Med Sci. 2013;68:608–16.
127. Ogawa T, Spina RJ, Martin WH, Kohrt WM, Schechtman KB, Holloszy JO, et al. Effects of aging, sex, and physical training on cardiovascular responses to exercise. Circulation. 1992;86:494–503.
128. Irrcher I, Adhihetty PJ, Joseph AM, Ljubicic V, Hood DA. Regulation of mitochondrial biogenesis in muscle by endurance exercise. Sports Med. 2003;33:783–93.
129. Kang C, Ji LL. Role of PGC-1α in muscle function and aging. J Sports Health Sci. 2013;2:81–6.
130. Gavin TP, Ruster RS, Carrithers JA, Zwetsloot KA, Kraus RM, Evans CA, et al. No difference in the skeletal muscle angiogenic response to aerobic exercise training between young and aged men. J Physiol. 2007;585:231–9.
131. Iversen N, Krustrup P, Rasmussen HN, Rasmussen UF, Saltin B, Pilegaard H. Mitochondrial biogenesis and angiogenesis in skeletal muscle of the elderly. Exp Gerontol. 2011;46:670–8.
132. Pollock RD, O'Brien KA, Daniels LJ, Nielsen KB, Rowlerson A, Duggal NA, et al. Properties of the vastus lateralis muscle in relation to age and physiological function in master cyclists aged 55–79 years. Aging Cell. 2018;17:e12735.
133. Poole DC, Jones AM. Measurement of the maximum oxygen uptake VO_{2max}: VO_{2peak} is no longer acceptable. J Appl Physiol. 2017;122:997–1002.
134. Joyner MJ. Physiological limits to endurance exercise performance: influence of sex. J Physiol. 2017;595:2949–54.
135. Howden EJ, Perhonen M, Peshock RM, Zhang R, Arbab-Zadeh A, Adams-Huet B, et al. Females have a blunted cardiovascular response to one year of intensive supervised endurance training. J Appl Physiol. 2015;119:37–46.
136. Ingjer F. Maximal oxygen uptake as a predictor of performance ability in women and men elite cross-country skiers. Scand J Med Sci Sports. 1991;1:25–30.

Physical strategies for the prevention of disuse-induced functional decline in older adults

With the aim of examining the effectiveness of different physical strategies – including voluntary exercise and other potential passive alternatives for patients unable to voluntary exercise – in preventing disuse-induced functional decline in older adults, we performed a narrative review that was published in *Ageing Research Reviews (impact factor: 10.390, position:* position 2/53, category: Geriatrics).[54] A summary of the physical strategies that can be used to prevent disuse-induced functional decline in older adults is available in Figure 3.

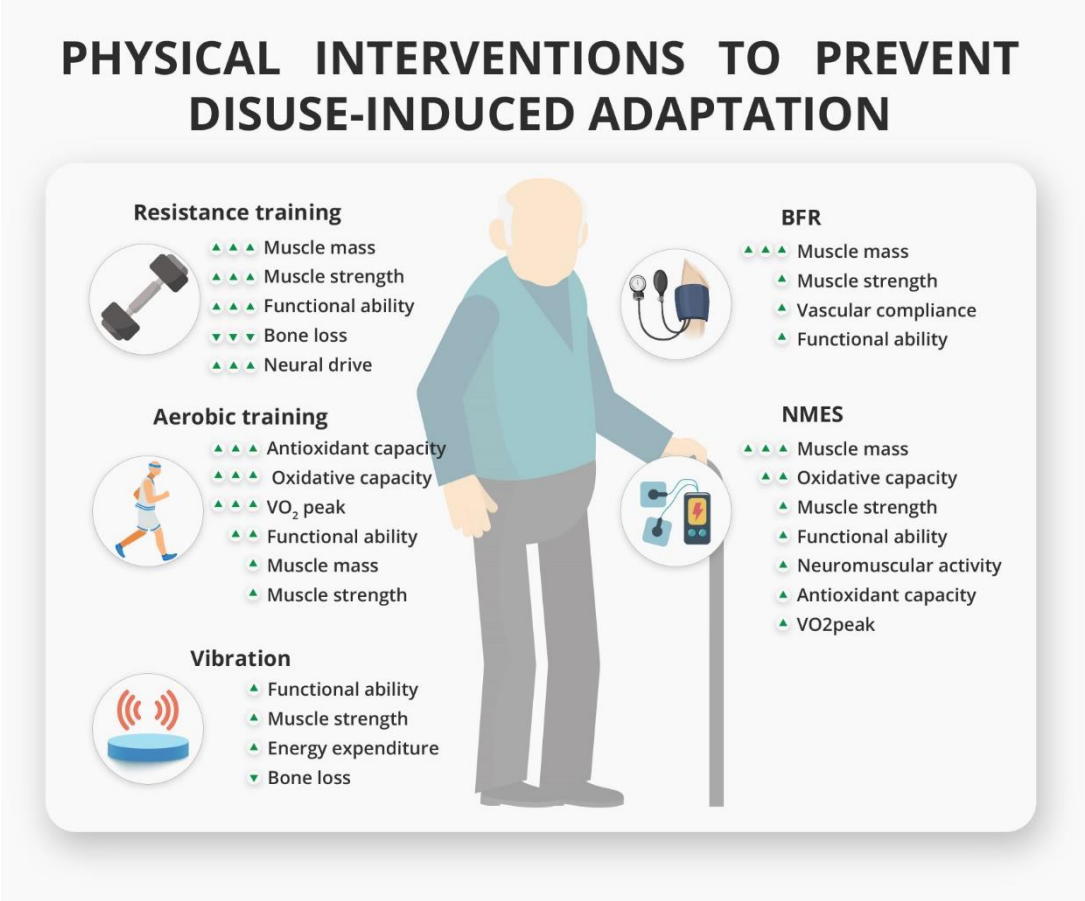


Figure 3. Summary of physical strategies that can be applied for the prevention of disuse-induced functional decline in older adults.

Ageing Research Reviews 47 (2018) 80–88

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Physical strategies to prevent disuse-induced functional decline in the elderly

Pedro L. Valenzuela[a,b,*,1], Javier S. Morales[c,1], Helios Pareja-Galeano[c,d], Mikel Izquierdo[e,f,h], Enzo Emanuele[g], Pedro de la Villa[a], Alejandro Lucia[c,d,f]

[a] Department of Systems Biology, University of Alcalá, Madrid, Spain
[b] Department of Sport and Health, Spanish Agency for Health Protection in Sport (AEPSAD), Madrid, Spain
[c] Universidad Europea de Madrid, Faculty of Sport Sciences, Madrid, Spain
[d] Research Institute of the Hospital 12 de Octubre ("i+12"), Madrid, Spain
[e] Department of Health Sciences, Public University of Navarra, Pamplona, Spain
[f] CIBER of Frailty and Healthy Aging (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain
[g] 2E Science, Robbio, Pavia, Italy
[h] Navarrabiomed, IdiSNA, Navarra Institute for Health Research, Pamplona, Navarra, Spain

ARTICLE INFO

Keywords:
Skeletal muscle
Rehabilitation
Ageing
Muscle wasting
Immobilization
Bed rest

ABSTRACT

Disuse situations can have serious adverse health consequences in the elderly, including mainly functional impairment with subsequent increase in the risk of falls or morbimortality. The present review provides clinicians and care givers with detailed and practical information on the feasibility and effectiveness of physical strategies that are currently available to prevent or attenuate the functional decline that occurs secondarily to disuse situations in the elderly, notably in the hospital setting. In this context, active approaches such as resistance exercises and maximal voluntary contractions, which can be performed both isometrically and dynamically, are feasible during most immobilization situations including in hospitalized old people and represent powerful tools for the prevention of muscle atrophy. Aerobic exercise should also be prescribed whenever possible to reduce the loss of cardiovascular capacity associated with disuse periods. Other feasible strategies for patients who are unwilling or unable to perform volitional exercise comprise neuromuscular electrical stimulation, vibration, and blood flow restriction. However, they should ideally be applied synchronously with voluntary exercise to obtain synergistic benefits.

1. Introduction

Maintaining functional ability or the so-called 'intrinsic capacity' (defined as the composite of physical and mental capacities of an individual) has recently been identified as the main goal to promote healthy ageing (Beard et al., 2016; Rodriguez-Mañas and Fried, 2015). In this regard, physical inactivity, notably bed rest, is a key factor contributing to the onset of functional ability decline in the elderly. Ten days of bed rest result in a marked reduction in muscle mass and strength, walking speed, and functional ability in old individuals (Coker et al., 2015), all these changes being related to a higher risk of health-related adverse events and mortality (Cooper et al., 2011, 2010; Ruiz et al., 2008; Srikanthan and Karlamangla, 2014). Although a loss of muscle mass, force, power, aerobic capacity and functional ability has been reported in both young and old subjects in response to bed rest periods, the magnitude of these alterations is comparatively greater in the latter, together with a slower return to pre-disuse conditions (Pišot et al., 2016). Even very short disuse periods, of only 5 days, are sufficient to elicit important negative consequences in old people, including a marked loss of muscle mass and strength, a suppression of protein synthesis and a slight increase in proteolytic markers (Dirks et al., 2014a; Tanner et al., 2015).

Muscle disuse has major clinical consequences. Almost half of the elderly patients hospitalized for a nondisabling condition suffer from a functional decline at discharge (which is maintained even after 1 month of follow-up) (Zisberg et al., 2011). Muscle disuse is associated with a worsened metabolic health (Wall et al., 2013), reduced glucose tolerance, and increased insulin resistance (Dirks et al., 2016). Furthermore,

* Corresponding author at: Physiology Unit, Department of Systems Biology, School of Medicine, University of Alcalá, Ctra. Barcelona, Km 33,600, 28871, Alcalá de Henares, Madrid, Spain.
E-mail address: pedrol.valenzuela@edu.uah.es (P.L. Valenzuela).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.arr.2018.07.003
Received 8 April 2018; Received in revised form 8 May 2018; Accepted 9 July 2018
Available online 18 July 2018

disuse-induced loss of muscle mass and strength affects postural muscles (Ikezoe et al., 2012), ultimately increasing the risk of falls and fractures (von Haehling et al., 2010). Elderly patients with lower muscle mass and strength are more likely to have longer hospital stays, and are at higher risk for readmission in the months following discharge, eventually resulting in increased hospitalization costs (Gani et al., 2016). In old people undergoing major abdominal surgery, sarcopenia is associated with a higher rate of death and postoperative complications (Gani et al., 2016; Gariballa and Alessa, 2013),

Physical activity levels in older adults are generally too low and sometimes almost null, especially during institutionalization or hospitalization (Nelson et al., 2007). Hospitalized older patients, including those able to walk independently, spend most of their hospital time in bed (Brown et al., 2009; Martínez-Velilla et al., 2013). This is an important fact because, in addition to deteriorating their functional status, bed rest increases the risk for cognitive decline and dementia in the elderly (Ehlenbach et al., 2010). Callen et al. (Callen et al., 2004) observed that nearly 75% of elderly subjects did not walk at all during hospitalization–with a median daily walking time as short as 5.5 min. Other studies reported that hospitalized elderly patients spend just ~5% of their daily time standing or walking (Pedersen et al., 2013; Villumsen et al., 2015). In this context, a recent systematic review including 17 randomized controlled trials found that the introduction of an exercise program for acutely hospitalized elderly patients is feasible and cost-effective, providing benefits in functional outcomes both after discharge and even one year later (Martínez-Velilla et al., 2016).

Although the physiopathology underlying the interplay of ageing and disuse-related muscle wasting remains to be clearly elucidated, several mechanisms have been postulated, notably reduction in myogenic capacity (Suetta et al., 2013), mitochondrial dysfunction with a subsequent increase in reactive oxygen species (Powers et al., 2012) and inflammation (Dalle et al., 2017). Regardless of the specific contribution of the aforementioned factors, muscle wasting eventually results from an imbalance between muscle protein synthesis and breakdown (Bodine, 2013). The pro-inflammatory state and physical inactivity that accompany disuse periods seem to lead to the activation of skeletal muscle proteolytic pathways (*i.e.*, autophagy and the ubiquitin-proteasome, and the calpain and caspase systems), but especially to a suppression of anabolic signaling pathways (Bodine, 2013; Phillips et al., 2009). Moreover, ageing has been related to skeletal muscle 'anabolic resistance', which in turn could be due to the suboptimal protein intake and sedentary behavior of this population segment (Shad et al., 2016). Disuse periods result in a further increase in anabolic resistance that is of greater magnitude in older than in young individuals (Biolo et al., 2017). Thus, the promotion of anabolic strategies such as physical activity and optimal amino acid/protein intake is mandatory in every population, but especially in the elderly one (Shad et al., 2016).

Several non-pharmacological strategies are available to prevent disuse-induced functional ability decline in the elderly. Nutritional interventions including protein supplementation have received the most attention for this purpose (Robinson et al., 2017; Wall and van Loon, 2013). Although nutrition plays a pivotal role in the prevention of functional decline in this population, the role of physical strategies such as exercise or the so-called 'exercise mimetics' should not be disregarded. The purpose of this review is to provide clinicians and care givers with updated information on the feasibility and effectiveness of those physical strategies that are currently available to prevent or attenuate the functional decline that occurs secondarily to disuse situations in the elderly (see Fig. 1 for a summary).

2. Physical strategies for the prevention of disuse-induced functional ability decline

2.1. Resistance training

Resistance training (RT) is a main strategy for improving physical function and preventing acute sarcopenia in elderly adults (Cadore et al., 2014c), as it can induce substantial gains in muscle mass and strength and provides a protective effect against several of the cellular and molecular changes associated with muscle wasting (Reeves et al., 2006). RT elicits the activation of anabolic signaling pathways (such as the mammalian target of rapamycin) by increasing mechanical and metabolic stress (Schoenfeld, 2013; Zanchi and Lancha, 2008), and promotes hypertrophy through an increased muscle protein synthesis (Damas et al., 2015).

A number of studies have demonstrated the potential of RT for preventing muscle wasting in elderly people, and improving their muscle strength mainly through increases in muscle volume and neural drive (Ferri et al., 2003; Morse et al., 2005; Reeves et al., 2004). Supporting the effectiveness of this strategy, a recent systematic review showed that RT performed alone or in combination with other different exercise modalities (*e.g.,* balance exercises) exerts positive effects on muscle mass (3.4–7.5%) and strength (6.6–37%), functional ability, and risk of falls (4.7–58.1%) in physically frail elderly adults (Lopez et al., 2017). We previously reported that even short-duration (8–12 weeks) and light- to moderate-intensity (20–70% of one-repetition maximum, 1RM) RT-based exercise interventions can increase muscle strength in institutionalized nonagenarians (Cadore et al., 2014a, b; Serra-Rexach et al., 2011). For instance, significant improvements in 1RM leg press (17% on average) were observed in the intervention group after short-duration (8 weeks) training (Serra-Rexach et al., 2011).

Different RT modalities (*e.g.,* isokinetic or isoinertial exercises) have been investigated in relation to their effectiveness for preventing disuse-induced muscle atrophy (Alkner and Tesch, 2004; Bamman et al., 1997) although their feasibility in the practical clinical context remains to be demonstrated. In contrast, a practical RT intervention performed in bed and including 'conventional' exercises (*e.g.*, single/bilateral leg extension, plantar/dorsiflexion) has proven feasible even shortly after hospitalization in elderly, acutely ill hospitalized patients (Mallery et al., 2003). Isometric exercises (*e.g.*, isometric leg press) can also be performed during bed rest by institutionalized and hospitalized elderly patients, and have proven effective for preventing loss of strength and muscle cross-sectional area (Akima et al., 2000; Kawakami et al., 2001). Similarly, dynamic exercises (*e.g.*, dynamic leg press) performed in bed are beneficial to prevent loss of muscle mass and strength during disuse periods (Akima et al., 2001, 2003), and can also attenuate the associated loss of bone mineral density (Shackelford et al., 2004).

Even more important than preventing loss of muscle strength (*i.e.*, force output) in the elderly is to prevent loss of muscle power (*i.e.*, work output per unit of time), because the latter decreases at a greater rate with ageing and is a more powerful predictor of functional disability (Reid and Fielding, 2012). RT programs aimed at improving muscle power (*i.e.*, including 'high-speed 'resistance exercises) are more effective for the improvement of lower-body muscle power and functionality than more traditional ('low-speed') programs (Ramírez-Campillo et al., 2014; Steib et al., 2010; Straight et al., 2016; Tschopp et al., 2011), and have proven feasible even in institutionalized oldest old frail individuals (Cadore et al., 2014a, b). For instance, 12 weeks of 'explosive' RT (8–10 repetitions at 40–60% of the 1RM and at the highest possible speed) in combination with balance exercises and gait retraining resulted in substantial gains in muscle power output (96–116%), strength (24–144%), muscle cross-sectional area and functional outcomes in frail institutionalized nonagenarians (Cadore et al., 2014a). Thus, although isometric or low-speed RT can be effective options for the prevention of acute sarcopenia in institutionalized

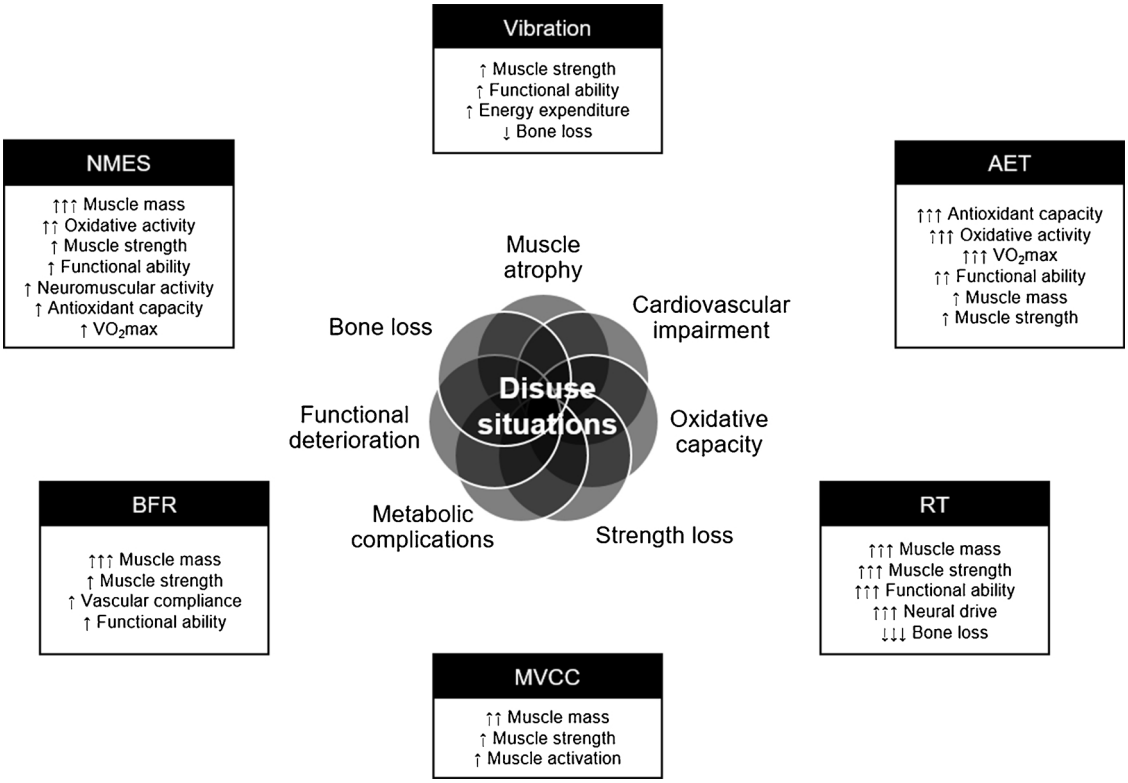


Fig. 1. Main adaptations in response to disuse situations and potential physical countermeasures. Abbreviations: AET, aerobic training; BFR, blood flow restriction; HSP, heat shock proteins; MVCC, maximal voluntary co-contraction; NMES, neuromuscular electrical stimulation; RT, resistance training; VO_2max, maximal oxygen uptake.

or hospitalized elderly patients, 'high-speed 'dynamic RT (with the concentric phase being performed as fast as possible) should be preferably recommended (Cadore and Izquierdo, 2018; Cadore et al., 2018).

In summary, traditional RT and especially muscle power training are effective options for retaining or even improving functional ability in the elderly population, including the oldest old and hospitalized or institutionalized individuals (Cadore and Izquierdo, 2018). RT programs should be ideally performed at least three times per week, with three sets of 8 to 12 repetitions at an intensity of 30%–40% of 1RM at the start of the program and progressing to 80% of 1RM by the end of it (Cadore et al., 2013). These interventions can be implemented in hospital rooms or nursing homes using machines, free weights or the own body as resistance (*e.g.,* raising from the chair as fast as possible). Specific RT programs can be designed even for elderly, acutely ill, hospitalized patients during bed rest (Mallery et al., 2003). In this context, simple exercises are feasible with elastic ('thera') bands attached to a hospital bed (targeting a rate of perceived load of 8 on a 0–10 scale, which can be modified by varying band resistance and range of motion) and result in high levels of muscle activity (Vinstrup et al., 2017). In fact, RT interventions using elastic bands (8–12 weeks, 2–5 days/week and 8–12 repetitions per session) have proven effective for the improvement of muscle strength and balance in institutionalized elderly subjects (Cho and An, 2014; Motalebi et al., 2018).

2.2. Endurance ('aerobic') training

Ageing gradually reduces maximum oxygen consumption (commonly abbreviated as 'VO_{2max}' [or VO_{2peak}] and assessed during incremental exercise testing involving large muscle mass [brisk walking/running, bicycling]). Age reductions in VO_{2max} are primarily linked to a decrease in cardiac output (Astrand et al., 1973) and low mitochondrial biogenesis and function (Gomez-Cabrera et al., 2012), but disuse situations elicit further, abrupt decreases in this variable (Capelli et al., 2006). A longitudinal study demonstrated that 3 weeks of bed rest result in a greater decline in VO_{2max} than 30 years of ageing (McGuire et al., 2001). Consequently, strategies aiming at improving VO_{2max} in elderly subjects and especially at attenuating its reduction during disuse situations should be part of the exercise routine.

Aerobic exercise training (AET) elicits the activation of signaling pathways involved in the improvement of oxidative capacity and mitochondrial biogenesis (Wiggs, 2015). This training modality also favors an endogenous antioxidant response (Powers et al., 2011) and increases the levels of heat shock proteins (HSPs), a group of molecular chaperones that facilitate protein synthesis and the repair of damaged proteins (Feder and Hofmann, 1999; Lawler et al., 2006; Senf et al., 2008). AET has been shown to elicit several benefits in non-immobilized elderly subjects (Cadore et al., 2013), including higher increases in VO_{2max} and peak working capacity during cycle-ergometer (Hagberg et al., 1989; Izquierdo et al., 2004) or treadmill exercise testing than those observed with RT (Hagberg et al., 1989; Izquierdo et al., 2004). In young (20–27 years) and older adults (60–75 years) with leg immobilization, AET can accelerate the recovery of functional capacity (by 33% and 20%, respectively) and strength (34% and 17%) (Vigelsø et al., 2015).

Although 5–10 min of AET might suffice during the first weeks, training duration should be progressively increased to a minimum of 15–30 min per day. Intensity should ideally start at 40–50% of maximum heart rate and gradually progress to reach 70–80% of maximum heart rate (Cadore et al., 2014c). AET may be performed in hospital rooms or geriatric residences with simple exercises such as step-ups, leg/arm stationary cycling or walking along a corridor, and it has also proven feasible and effective during bed rest. Performing AET in supine position with a cycle ergometer or a treadmill placed in a vertical position can be sufficient to avoid cardiovascular deterioration in subjects submitted to 15 days of bed rest (Watenpaugh et al., 2000). This type of

exercise has also been reported to improve the muscle strength (by ~30%) and functional capacity of critically ill patients (Burtin et al., 2009).

2.3. Maximal voluntary co-contraction

Maximal voluntary co-contraction (MVCC), also known as 'antagonist resisted training', comprises the simultaneous volitional contraction of antagonistic muscle groups. Because the opposite resistive forces exerted by the contracted muscles nullify each other, no external loads or even articular movements are required. Thus, MVCC training can be easily applied in any context, and is especially suitable for immobilized patients (Jaafar, 2016).

MVCC training elicits important levels of muscle activation (~40–70% of the maximal voluntary contraction [MVC]) in healthy subjects (Maeo et al., 2013; Serrau et al., 2012). Albeit of lower magnitude than those produced by an isometric contraction against external opposition (Serrau et al., 2012), these activation levels are sufficient to induce beneficial muscular adaptations. Performing isometric MVCC with the elbow placed at 90 degrees (*e.g.*, 5 sets of 10 repetitions of 4-second muscle co-contractions) has been shown to improve muscle mass and strength (Driss et al., 2014; Maeo et al., 2014a, b). For instance, Maeo et al. (2014a, 2014b) found a 15% and 46% increase in the MVC of elbow flexors and extensors, respectively, and an increased muscle thickness of these muscle groups (4% for both) after 12 weeks of MVCC training, whereas no gains were observed in the control group (Maeo et al., 2014b). MacKenzie et al. (2010) found that 6 weeks of dynamic MVCC (elbow flexion and extensions lasting 4 s each) with one arm increased elbow flexion (5.8%) and extension (8.5%) strength compared to the contra-lateral inactive control arm (0.5 and 4.5% change, respectively) (MacKenzie et al., 2010). Moreover, biceps and triceps muscle activation in response to a MVC increased more in the trained (30.1 and 61.1%, respectively) than in the untrained arm (9.2 and 1.1%, respectively). Recent evidence indicates that MVCC training is as effective as high-load dynamic RT (70% of 1RM) for increasing muscle mass in untrained subjects, although the latter would induce greater gains (improvements of 2.3 *vs.* 1.0 kg in 1RM) in muscle strength (Counts et al., 2016).

Despite the lack of specific evidence supporting the effectiveness of MVCC in elderly patients or disuse situations, the aforementioned promising results prompt further studies on the clinical utility of this strategy for preventing muscle atrophy during bed rest or limb immobilization. As with isometric RT, there is a traditional concern about potential negative acute effects of MVCC on blood pressure (Chrysant, 1978). Notwithstanding, isometric contractions have proven effective for the management of hypertension (Inder et al., 2016). It is also important to note that muscular activation level during MVCC may depend on the difference in maximal strength between agonistic and antagonistic muscles. For this reason, this strategy might be ineffective if there is a great imbalance in strength between muscles, as occurs in some leg muscles (*e.g.*, plantar flexor and extensors) (Maeo and Kanehisa, 2014).

2.4. Blood flow restriction

Although elderly individuals should ideally perform high-intensity RT to maximize training-induced adaptations, this form of training may not be feasible for some hospitalized or institutionalized frail elderly patients. Blood flow restriction (BFR, also known as KAATSU) is accomplished by inflating a cuff around the proximal part of the target limb to a pressure that blocks venous blood return but not arterial inflow into the muscle (Loenneke et al., 2012b). This strategy induces an increase in anabolic hormones as a result of an increased metabolic stress (Inagaki et al., 2011; Takano et al., 2005), ultimately facilitating protein synthesis (Fujita et al., 2007; Wernbom et al., 2013) and increasing HSP levels (Kawada and Ishii, 2005).

Meta-analytical evidence supports the effectiveness of BFR for increasing muscle mass and strength (Loenneke et al., 2012c; Slysz et al., 2016). In accordance with the potential benefits of this strategy for institutionalized and hospitalized elderly patients, a meta-analysis concluded that the application of BFR together with low-intensity exercise (*e.g.,* RT with elastic bands or < 20% of 1RM, or low-intensity AET) is more effective than low-intensity exercise alone for increasing muscle strength in clinical populations at risk of muscle wasting, such as the elderly (Hughes et al., 2017). The combination of BFR and low intensity exercise has also proven effective to stimulate anabolic signaling pathways and improve muscle mass/strength in elderly subjects (Fry et al., 2010; Ozaki et al., 2011; Yasuda et al., 2014). Further, similar gains in lower-limb muscle mass have been observed in older individuals with high-intensity RT alone than with low-intensity RT performed with BFR (Vechin et al., 2015), albeit gains in muscle strength were lower with the latter (Karabulut et al., 2010; Vechin et al., 2015). Low-load RT combined with BFR is also effective for the prevention of muscle loss and weakness after 30 days of unilateral lower limb suspension (Cook et al., 2010). BFR combined with light AET (walking, cycling) improves vascular compliance in the elderly (Iida et al., 2011; Ozaki et al., 2011), which is an important finding because this variable markedly decreases with ageing or bed rest (Bleeker et al., 2004). In addition, it improves muscle size, strength and functional ability to a greater extent than a higher volume of AET without BFR (Abe et al., 2010).

BFR seems to be especially useful when applied simultaneously with physical exercise (Loenneke et al., 2012c). BFR in conjunction with low intensity exercise may be a feasible and effective training strategy for attenuating muscle wasting and functional ability (Abe et al., 2010) in those subjects with greater difficulties to perform high intensity exercise. Notwithstanding, some benefits (reductions in muscle mass/strength loss) have also been observed with BFR alone (*i.e.,* without exercise) in young subjects during knee immobilization (Kubota et al., 2011, 2008; Takarada et al., 2000), which suggests that BFR could also be a promising strategy to be applied in any situation, or in people who are unable to perform volitional exercise.

Some methodological issues must be however remarked. The BFR stimulus should be individualized and progressively increased by adjusting the restrictive pressure or the cuff width (Scott et al., 2015). Wider cuffs (6–13.5 cm) are recommended for the legs than for the arms (3–6 cm), although it is also of note that wider cuffs achieve occlusion at lower pressures (Scott et al., 2015). BFR pressure should be high enough to occlude venous return, yet without impairing arterial inflow. The optimal pressure varies between individuals depending on different factors, notably limb girth (with larger limbs requiring higher pressure). A BFR pressure corresponding to 50–80% of the arterial occlusion pressure has been recommended (Scott et al., 2015). However, other practical methods such as targeting a score of 7 on a perceived pressure scale ranging from 0 to 10 (with 0 indicating no pressure and 10 indicating intense pressure) could be a less accurate but feasible option in some clinical settings (Wilson et al., 2013). It would be advisable to perform a progression from the application of BFR alone (during the first stages of bed rest) to its application in conjunction with light AET (20 min of walking or cycling) or low-load RT (3–5 sets at 20–40% of 1RM, targeting a total of 50–80 repetitions per exercise, with inter-set rests of 30–45 s in which occlusion is maintained) to maximize adaptations (Loenneke et al., 2012a; Scott et al., 2015).

2.5. Neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMES) consists of the application of high-intensity and intermittent electrical stimuli to generate involuntary muscle contractions. This strategy has been proposed as an "exercise simulator", with *i)* low-frequency NMES activating the same signaling pathway as AET and *ii)* high-frequency NMES activating the same signaling pathway as RT (Atherton et al., 2005). NMES induces a

synchronic recruitment of muscle fibers independently of their contractile/metabolic phenotype, and as such high loads are not needed to recruit type II, glycolytic fibers (Bickel et al., 2011). Although it is generally thought that NMES bypasses the central nervous system, the electrically-evoked contraction activates corticomotor pathways that are similar to those activated by voluntary contractions (Blickenstorfer et al., 2009; Francis et al., 2009). In fact, NMES increases electromyographic activity and neural activation (Maffiuletti et al., 2002). Voluntary physical exercise should be performed whenever possible. However, NMES has the potential to be used for rehabilitation purposes, especially in those individuals who cannot perform volitional exercise – including frail older adults and hospitalized patients (Caggiano et al., 1994; Maffiuletti et al., 2018; Paillard, 2018).

Several studies have reported that NMES exerts beneficial effects on muscle strength and functionality in different clinical populations (*e.g.,* pre-frail and long-stay hospitalized elderly individuals) (Maggioni et al., 2010; Mignardot et al., 2015). A recent systematic review showed that NMES is an effective strategy to improve muscle mass/strength in adults with advanced disease and muscle weakness (Jones et al., 2016). NMES has also proven to attenuate the functional decline associated with ageing, ultimately improving muscle mass/strength and performance in functional tests that are indicative of frailty and risk of falls (Kern et al., 2014). Moreover, NMES has been shown effective to prevent the reduction of muscle mass and strength after lower-limb injuries (Delitto et al., 1988; Gibson et al., 1988; Taradaj et al., 2013), as well as to increase muscle protein synthesis and attenuate the loss of muscle mass/strength and oxidative enzymatic capacity during disuse situations such as bed rest or limb immobilization (Dirks et al., 2014b; Duvoisin et al., 1989). NMES has also been recently reported to mitigate the loss of muscle mass and strength in critically ill patients (Maffiuletti et al., 2013), including those with consciousness disturbances (*e.g.,* coma, stroke brain injury) (Hirose et al., 2013).

In addition to muscle mass and strength, NMES can also increase endurance performance in clinical populations (Veldman et al., 2016), resulting in an amelioration of muscular oxidative capacity (Erickson et al., 2016; Ryan et al., 2013) and VO_2max (Lee et al., 2012; Vaquero et al., 1998). Finally, and similar to endurance training, NMES seems to increase antioxidant capacity (Gondin et al., 2011), being therefore potentially useful to reduce the redox imbalance elicited by disuse periods (Pellegrino et al., 2011).

Some practical recommendations have been made in order to achieve a higher effectiveness of NMES for preserving muscle mass and function in the clinical context (Maffiuletti et al., 2018). NMES sessions used for the prevention of muscle weakness and wasting typically last 30–60 min (Maffiuletti et al., 2013). It has been proposed that stimulation frequencies and pulse (biphasic rectangular pulses) durations should range between 50–75 Hz and 100–400 μs, respectively, and the intensity applied should be the highest tolerable to maximize force production (*i.e.*, ~25–50% of MVC, although expressing the NMES-evoked force as a fraction of MVC force is not always appropriate, especially in weak patients) as there is a dose-response relationship between NMES training intensity and NMES effectiveness (Maffiuletti et al., 2018). A high volume (*i.e.*, every day, or even several times per day) of NMES is recommended in patients with pronounced activation deficits (*e.g.*, early after knee surgery), but a low-volume (*i.e.*, alternate days) high-intensity approach should be adopted to target muscle hypertrophy once neural deficits have resolved (Maffiuletti et al., 2018). Although NMES is usually delivered passively, it can also be applied superimposed onto voluntary physical exercise, potentially resulting in higher motor unit recruitment in comparison with the latter alone. There is controversy with regards to fit people, but superimposed NMES seems more effective than voluntary exercise alone in untrained subjects or clinical populations (Paillard et al., 2005).

In summary, although voluntary physical activity (*e.g.,* RT) is likely to be the most effective intervention to improve muscle function (Suetta et al., 2008, 2004), it may not be feasible for specific populations (frail older adults) or situations (bed rest, limb immobilization, general weakness). In this context, NMES training appears as a feasible, effective strategy to combat muscle disuse atrophy (Dirks et al., 2017; Maffiuletti et al., 2018; Paillard, 2018).

2.6. Vibration

This strategy consists of applying a mechanical oscillation (*i.e.*, periodic alteration of force, acceleration and displacement) from a vibration device to either the whole body (while standing on a vibratory platform) or some parts of it (local vibration applied superficially over the targeted areas) (Rittweger, 2010). The potential of vibration to increase muscle mass and performance in healthy subjects has been previously discussed (Nordlund and Thorstensson, 2007). Notably, this technique has gained popularity in geriatric rehabilitation during the last decade. Vibration may promote bone anabolism (Rubin et al., 2001) and evoke an involuntary muscle contraction through the activation of stretch reflexes (Abercromby et al., 2007; Falempin and In-Albon, 1999). Consequently, this strategy could be useful to mitigate muscle and bone loss occurring during immobilization periods or in subjects with difficulties performing volitional exercise (such as the elderly).

Whole-body vibration is a safe and feasible strategy to improve balance and mobility in nursing home residents (Bautmans et al., 2005). Recent evidence also shows its safety and feasibility in critically ill patients, resulting in an increased energy expenditure (Wollersheim et al., 2017). Interestingly, a higher increase in anabolic hormones (*e.g.*, insulin growth factor-1) has been observed in elderly subjects performing exercise in combination with whole-body vibration compared to the same exercise alone (Cardinale et al., 2010). In addition, 12 weeks of local vibration (one to three 15-minute sessions per week at 300 Hz) applied to the quadriceps muscles has been demonstrated to counteract loss of muscular strength (140–180% increase in isometric strength of the knee extensor muscles) associated with sarcopenia in elderly people (Pietrangelo et al., 2009). Different systematic reviews and meta-analyses have concluded that whole-body vibration is effective to enhance muscle strength, postural control and balance in this population (Lau et al., 2011; Rogan et al., 2017; Sitjà-Rabert et al., 2012). However, the benefits may not be as remarkable as those observed with conventional voluntary exercise (Sitjà-Rabert et al., 2012). Meta-analytical evidence also supports the role of this strategy for the prevention of bone loss in the lumbar spine of elderly women (Ma et al., 2016; Oliveira et al., 2016). In addition, it has been shown to reduce the negative changes at a spinal level occurring during 90 days of bed rest in young subjects (Holguin et al., 2009), and could be more effective than walking to improve balance and hip bone mineral density in elderly women (Gusi et al., 2006).

Although whole-body vibration training has proven overall safe, ineffective or unnecessary large exposures should be avoided to prevent potential detrimental effects in older people (such as low back pain) (Brooke-Wavell and Mansfield, 2009). Most studies have applied three or more sessions per week of a few bouts lasting between one and two minutes and with frequencies of 20–45 Hz (Rittweger, 2010). Some evidence suggests that a higher myoelectric activity could be achieved with higher amplitudes (4 mm) and frequencies (60 Hz) (Krol et al., 2011). It has been proposed that, in order to avoid excessive resonance, frequencies around or below 5 Hz should be avoided, and caution should be taken with frequencies below 20 Hz (Rittweger, 2010). Vibration transmission can also be reduced by decreasing vibration amplitude and flexing the knees or alternating sides instead of applying synchronous vibration (Rittweger, 2010). There is, however, no evidence as to the optimal vibration protocol.

The combination of vibration and RT can provide several benefits in frail elderly subjects and during disuse situations, including an attenuation in loss of bone mass or muscle mass/strength (Rittweger, 2010). However, as most studies applied both stimuli synchronously, it

is difficult to assess the effect of the vibration method individually. Some authors have analyzed whether the addition of vibration to RT during immobilization periods could provide additional benefits compared to RT alone. Although the benefits observed on muscle atrophy with the former could be similar to those obtained with RT alone (Miokovic et al., 2014), additional benefits could be observed in terms of bone mineral density when the vibratory stimulus and RT are combined (Belavý et al., 2011). This strategy should therefore be considered in frail elderly subjects–especially in combination with voluntary RT.

3. Conclusion

Conditions leading to inactivity (*e.g.,* hospitalization, acute illness) exacerbate the natural process of sarcopenia in elderly people and result in functional decline, which has important clinical consequences. In this context, physical activity programs play a pivotal role for attenuating or preventing functional decline, and should therefore be routinely included in at-risk populations such as institutionalized and hospitalized old patients.

RT appears as the most powerful stimulus for the prevention of bone loss, neuromuscular degeneration and overall functional decline in the elderly. Although traditional RT has proven effective, muscle power training (*i.e.*, RT performed dynamically and at high speeds) should be preferably performed when possible. Benefits can also be obtained with RT performed isometrically, which makes it easily applicable during immobilization periods. Although more research in the elderly is needed, MVCC training could provide remarkable benefits and does not require external loads or even articular movement. Notwithstanding, RT should be ideally accompanied by AET, which can be also performed during bed rest.

Although voluntary exercise should be performed whenever possible, its application may be more problematic in some specific condition such as limb immobilization or general weakness. In these cases, NMES or vibration appear like suitable alternative strategies. Nevertheless, as far as possible it would be advisable to perform a progression of the applied stimuli and ultimately apply all of these strategies in conjunction with voluntary exercise.

Acknowledgments

PLV is supported by a predoctoral contract granted by the University of Alcalá (FPI2016). JSM is supported by a predoctoral contract granted by Ministry of Education, Culture and Sport (FPU14/03435). AL is supported by grants from Spanish Ministry of Economy and Competitiveness (Fondo de Investigaciones Sanitarias [FIS] and Fondos FEDER, grant number PI15/00558). HPG is supported by grant from Universidad Europea de Madrid (2017/UEM05) and Cátedra Real Madrid-Universidad Europea (2017/RM03). Mikel Izquierdo is supported by grants from from Spanish Ministry of Economy and Competitiveness (Fondo de Investigaciones Sanitarias [FIS] and Fondos FEDER, grant number PI17/01814). The authors declare no conflicts of interest.

References

Abe, T., Sakamaki, M., Fujita, S., Ozaki, H., Sugaya, M., Sato, Y., Nakajima, T., 2010. Effects of low-intensity walk training with restricted leg blood flow on muscle strength and aerobic capacity in older adults. J. Geriatr. Phys. Ther. 33, 34–40.

Abercromby, A.F., Amonette, W.E., Layne, C.S., McFarlin, B.K., Hinman, M.R., Paloski, W.H., 2007. Variation in neuromuscular responses during acute whole-body vibration exercise. Med. Sci. Sports Exerc. 39, 1642–1650.

Akima, H., Kubo, K., Kanehisa, H., Suzuki, Y., Gunji, A., Fukunaga, T., 2000. Leg-press resistance training during 20 days of 6 degrees head-down-tilt bed rest prevents muscle deconditioning. Eur. J. Appl. Physiol. 82, 30–38.

Akima, H., Kubo, K., Imai, M., Kanehisa, H., Suzuki, Y., Gunji, A., Fukunaga, T., 2001. Inactivity and muscle: effect of resistance training during bed rest on muscle size in the lower limb. Acta Physiol. Scand. 172, 269–278.

Akima, H., Ushiyama, J., Kubo, J., Tonosaki, S., Itoh, M., Kawakami, Y., Fukuoka, H., Kanehisa, H., Fukunaga, T., 2003. Resistance training during unweighting maintains muscle size and function in human calf. Med. Sci. Sports Exerc. 35, 655–662.

Alkner, B.A., Tesch, P.A., 2004. Efficacy of a gravity-independent resistance exercise device as a countermeasure to muscle atrophy during 29-day bed rest. Acta Physiol. Scand. 181, 345–357.

Astrand, I., Astrand, P.O., Hallbäck, I., Kilbom, A., 1973. Reduction in maximal oxygen uptake with age. J. Appl. Physiol. 35, 649–654.

Atherton, P.J., Babraj, J., Smith, K., Singh, J., Rennie, M.J., Wackerhage, H., 2005. Selective activation of AMPK-PGC-1alpha or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. FASEB J. 19, 786–788.

Bamman, M.M., Hunter, G.R., Stevens, B.R., Guilliams, M.E., Greenisen, M.C., 1997. Resistance exercise prevents plantar flexor deconditioning during bed rest. Med. Sci. Sports Exerc. 29, 1462–1468.

Bautmans, I., Van Hees, E., Lemper, J.C., Mets, T., 2005. The feasibility of Whole Body Vibration in institutionalised elderly persons and its influence on muscle performance, balance and mobility: a randomised controlled trial [ISRCTN62535013]. BMC Geriatr. 5, 17.

Beard, J.R., Officer, A., de Carvalho, I.A., Sadana, R., Pot, A.M., Michel, J.P., Lloyd-Sherlock, P., Epping-Jordan, J.E., Peeters, G.M.E.E., Mahanani, W.R., Thiyagarajan, J.A., Chatterji, S., 2016. The World report on ageing and health: a policy framework for healthy ageing. Lancet 387, 2145–2154.

Belavý, D.L., Beller, G., Armbrecht, G., Perschel, F.H., Fitzner, R., Bock, O., Börst, H., Degner, C., Gast, U., Felsenberg, D., 2011. Evidence for an additional effect of whole-body vibration above resistive exercise alone in preventing bone loss during prolonged bed rest. Osteoporos. Int. 22, 1581–1591.

Bickel, C.S., Gregory, C.M., Dean, J.C., 2011. Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal. Eur. J. Appl. Physiol. 111, 2399–2407.

Biolo, G., Pišot, R., Mazzucco, S., Di Girolamo, F.G., Situlin, R., Lazzer, S., Grassi, B., Reggiani, C., Passaro, A., Rittweger, J., Gasparini, M., Šimunič, B., Narici, M., 2017. Anabolic resistance assessed by oral stable isotope ingestion following bed rest in young and older adult volunteers: relationships with changes in muscle mass. Clin. Nutr. 36, 1420–1426.

Bleeker, M.W., De Groot, P.C., Pawelczyk, J.A., Hopman, M.T., Levine, B.D., 2004. Effects of 18 days of bed rest on leg and arm venous properties. J. Appl. Physiol. 96, 840–847.

Blickenstorfer, A., Kleiser, R., Keller, T., Keisker, B., Meyer, M., Riener, R., Kollias, S., 2009. Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. Hum. Brain Mapp. 30, 963–975.

Bodine, S.C., 2013. Disuse-induced muscle wasting. Int. J. Biochem. Cell Biol. 45, 2200–2208.

Brooke-Wavell, K., Mansfield, N.J., 2009. Risks and benefits of whole body vibration training in older people. Age Ageing 38, 254–255.

Brown, C.J., Redden, D.T., Flood, K.L., Allman, R.M., 2009. The underrecognized epidemic of low mobility during hospitalization of older adults. J. Am. Geriatr. Soc. 57, 1660–1665.

Burtin, C., Clerckx, B., Robbeets, C., Ferdinande, P., Langer, D., Troosters, T., Hermans, G., Decramer, M., Gosselink, R., 2009. Early exercise in critically ill patients enhances short-term functional recovery. Crit. Care Med. 37, 2499–2505.

Cadore, E.L., Izquierdo, M., 2018. Muscle power training: a hallmark for muscle function retaining in frail clinical setting. J. Am. Med. Dir. Assoc. 19, 190–192.

Cadore, E.L., Rodríguez-Mañas, L., Sinclair, A., Izquierdo, M., 2013. Effects of different exercise interventions on risk of falls, gait ability, and balance in physically frail older adults: a systematic review. Rejuvenation Res. 16, 105–114.

Cadore, E.L., Casas-Herrero, A., Zambom-Ferraresi, F., Idoate, F., Millor, N., Gómez, M., Rodriguez-Mañas, L., Izquierdo, M., 2014a. Multicomponent exercises including muscle power training enhance muscle mass, power output, and functional outcomes in institutionalized frail nonagenarians. Age (Dordr.) 36, 773–785.

Cadore, E.L., Moneo, A.B., Mensat, M.M., Muñoz, A.R., Casas-Herrero, A., Rodriguez-Mañas, L., Izquierdo, M., 2014b. Positive effects of resistance training in frail elderly patients with dementia after long-term physical restraint. Age (Dordr.) 36, 801–811.

Cadore, E.L., Pinto, R.S., Bottaro, M., Izquierdo, M., 2014c. Strength and endurance training prescription in healthy and frail elderly. Aging Dis. 5, 183–195.

Cadore, E.L., Pinto, R.S., Reischak-Oliveira, Á., Izquierdo, M., 2018. Explosive type of contractions should not be avoided during resistance training in elderly. Exp. Gerontol. 102, 81–83.

Caggiano, E., Emrey, T., Shirley, S., Craik, R.L., 1994. Effects of electrical stimulation or voluntary contraction for strengthening the quadriceps femoris muscles in an aged male population. J. Orthop. Sports Phys. Ther. 20, 22–28.

Callen, B.L., Mahoney, J.E., Grieves, C.B., Wells, T.J., Enloe, M., 2004. Frequency of hallway ambulation by hospitalized older adults on medical units of an academic hospital. Geriatr. Nurs. 25, 212–217.

Capelli, C., Antonutto, G., Kenfack, M.A., Cautero, M., Lador, F., Moia, C., Tam, E., Ferretti, G., 2006. Factors determining the time course of VO2(max) decay during bedrest: implications for VO2(max) limitation. Eur. J. Appl. Physiol. 98, 152–160.

Cardinale, M., Soiza, R.L., Leiper, J.B., Gibson, A., Primrose, W.R., 2010. Hormonal responses to a single session of wholebody vibration exercise in older individuals. Br. J. Sports Med. 44, 284–288.

Cho, S.I., An, D.H., 2014. Effects of a fall prevention exercise program on muscle strength and balance of the old-old elderly. J. Phys. Ther. Sci. 26, 1771–1774.

Chrysant, S.G., 1978. Hemodynamic effects of isometric exercise in normotensive and hypertensive subjects. Angiology 29, 379–385.

Coker, R.H., Hays, N.P., Williams, R.H., Wolfe, R.R., Evans, W.J., 2015. Bed rest promotes reductions in walking speed, functional parameters, and aerobic fitness in older, healthy adults. J. Gerontol. A Biol. Sci. Med. Sci. 70, 91–96.

Cook, S.B., Brown, K.A., Deruisseau, K., Kanaley, J.A., Ploutz-Snyder, L.L., 2010. Skeletal

muscle adaptations following blood flow-restricted training during 30 days of muscular unloading. J. Appl. Physiol. 109, 341–349.
Cooper, R., Kuh, D., Hardy, R., Group, M.R., Teams, Fa.H.S., 2010. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ 341, c4467.
Cooper, R., Kuh, D., Cooper, C., Gale, C.R., Lawlor, D.A., Matthews, F., Hardy, R., Teams, Fa.H.S., 2011. Objective measures of physical capability and subsequent health: a systematic review. Age Ageing 40, 14–23.
Counts, B.R., Buckner, S.L., Dankel, S.J., Jessee, M.B., Mattocks, K.T., Mouser, J.G., Laurentino, G.C., Loenneke, J.P., 2016. The acute and chronic effects of "NO LOAD" resistance training. Physiol. Behav. 164, 345–352.
Dalle, S., Rossmeislova, L., Koppo, K., 2017. The role of inflammation in age-related Sarcopenia. Front. Physiol. 8, 1045.
Damas, F., Phillips, S., Vechin, F.C., Ugrinowitsch, C., 2015. A review of resistance training-induced changes in skeletal muscle protein synthesis and their contribution to hypertrophy. Sports Med. 45, 801–807.
Delitto, A., McKowen, J.M., McCarthy, J.A., Shively, R.A., Rose, S.J., 1988. Electrically elicited co-contraction of thigh musculature after anterior cruciate ligament surgery. A description and single-case experiment. Phys. Ther. 68, 45–50.
Dirks, M.L., Wall, B.T., Nilwik, R., Weerts, D.H., Verdijk, L.B., van Loon, L.J., 2014a. Skeletal muscle disuse atrophy is not attenuated by dietary protein supplementation in healthy older men. J. Nutr. 144, 1196–1203.
Dirks, M.L., Wall, B.T., Snijders, T., Ottenbros, C.L., Verdijk, L.B., van Loon, L.J., 2014b. Neuromuscular electrical stimulation prevents muscle disuse atrophy during leg immobilization in humans. Acta Physiol. (Oxf.) 210, 628–641.
Dirks, M.L., Wall, B.T., van de Valk, B., Holloway, T.M., Holloway, G.P., Chabowski, A., Goossens, G.H., van Loon, L.J., 2016. One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. Diabetes 65, 2862–2875.
Dirks, M.L., Wall, B.T., van Loon, L.J.C., 2017. Interventional strategies to combat muscle disuse atrophy in humans: focus on neuromuscular electrical stimulation and dietary protein. J. Appl. Physiol jap.00985.02016.
Driss, T., Serrau, V., Behm, D.G., Lesne-Chabran, E., Le Pellec-Muller, A., Vandewalle, H., 2014. Isometric training with maximal co-contraction instruction does not increase co-activation during exercises against external resistances. J. Sports Sci. 32, 60–69.
Duvoisin, M.R., Convertino, V.A., Buchanan, P., Gollnick, P.D., Dudley, G.A., 1989. Characteristics and preliminary observations of the influence of electromyostimulation on the size and function of human skeletal muscle during 30 days of simulated microgravity. Aviat. Space Environ. Med. 60, 671–678.
Ehlenbach, W.J., Hough, C.L., Crane, P.K., Haneuse, S.J., Carson, S.S., Curtis, J.R., Larson, E.B., 2010. Association between acute care and critical illness hospitalization and cognitive function in older adults. JAMA 303, 763–770.
Erickson, M.L., Ryan, T.E., Backus, D., McCully, K.K., 2016. Endurance neuromuscular electrical stimulation training improves skeletal muscle oxidative capacity in individuals with motor-complete spinal cord injury. Muscle Nerve.
Falempin, M., In-Albon, S.F., 1999. Influence of brief daily tendon vibration on rat soleus muscle in non-weight-bearing situation. J. Appl. Physiol. 87, 3–9.
Feder, M.E., Hofmann, G.E., 1999. Heat-shock proteins, molecular chaperones, and the stress response: evolutionary and ecological physiology. Annu. Rev. Physiol. 61, 243–282.
Ferri, A., Scaglioni, G., Pousson, M., Capodaglio, P., Van Hoecke, J., Narici, M.V., 2003. Strength and power changes of the human plantar flexors and knee extensors in response to resistance training in old age. Acta Physiol. Scand. 177, 69–78.
Francis, S., Lin, X., Aboushoushah, S., White, T.P., Phillips, M., Bowtell, R., Constantinescu, C.S., 2009. fMRI analysis of active, passive and electrically stimulated ankle dorsiflexion. Neuroimage 44, 469–479.
Fry, C.S., Glynn, E.L., Drummond, M.J., Timmerman, K.L., Fujita, S., Abe, T., Dhanani, S., Volpi, E., Rasmussen, B.B., 2010. Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. J. Appl. Physiol. 108, 1199–1209.
Fujita, S., Abe, T., Drummond, M.J., Cadenas, J.G., Dreyer, H.C., Sato, Y., Volpi, E., Rasmussen, B.B., 2007. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. J. Appl. Physiol. 103, 903–910.
Gani, F., Buettner, S., Margonis, G.A., Sasaki, K., Wagner, D., Kim, Y., Hundt, J., Kamel, I.R., Pawlik, T.M., 2016. Sarcopenia predicts costs among patients undergoing major abdominal operations. Surgery 160, 1162–1171.
Gariballa, S., Alessa, A., 2013. Sarcopenia: prevalence and prognostic significance in hospitalized patients. Clin. Nutr. 32, 772–776.
Gibson, J.N., Smith, K., Rennie, M.J., 1988. Prevention of disuse muscle atrophy by means of electrical stimulation: maintenance of protein synthesis. Lancet 2, 767–770.
Gomez-Cabrera, M.C., Sanchis-Gomar, F., Garcia-Valles, R., Pareja-Galeano, H., Gambini, J., Borras, C., Viña, J., 2012. Mitochondria as sources and targets of damage in cellular aging. Clin. Chem. Lab. Med. 50, 1287–1295.
Gondin, J., Brocca, L., Bellinzona, E., D'Antona, G., Maffiuletti, N.A., Miotti, D., Pellegrino, M.A., Bottinelli, R., 2011. Neuromuscular electrical stimulation training induces atypical adaptations of the human skeletal muscle phenotype: a functional and proteomic analysis. J. Appl. Physiol. 110, 433–450.
Gusi, N., Raimundo, A., Leal, A., 2006. Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: a randomized controlled trial. BMC Musculoskelet. Disord. 7, 92.
Hagberg, J.M., Graves, J.E., Limacher, M., Woods, D.R., Leggett, S.H., Cononie, C., Gruber, J.J., Pollock, M.L., 1989. Cardiovascular responses of 70- to 79-yr-old men and women to exercise training. J. Appl. Physiol. 66, 2589–2594.
Hirose, T., Shiozaki, T., Shimizu, K., Mouri, T., Noguchi, K., Ohnishi, M., Shimazu, T., 2013. The effect of electrical muscle stimulation on the prevention of disuse muscle atrophy in patients with consciousness disturbance in the intensive care unit. J. Crit. Care 28 (536), e531–e537.
Holguin, N., Muir, J., Rubin, C., Judex, S., 2009. Short applications of very low-magnitude vibrations attenuate expansion of the intervertebral disc during extended bed rest. Spine J. 9, 470–477.
Hughes, L., Paton, B., Rosenblatt, B., Gissane, C., Patterson, S.D., 2017. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. Br. J. Sports Med. 51 (13), 1003–1011.
Iida, H., Nakajima, T., Kurano, M., Yasuda, T., Sakamaki, M., Sato, Y., Yamasoba, T., Abe, T., 2011. Effects of walking with blood flow restriction on limb venous compliance in elderly subjects. Clin. Physiol. Funct. Imaging 31, 472–476.
Ikezoe, T., Mori, N., Nakamura, M., Ichihashi, N., 2012. Effects of age and inactivity due to prolonged bed rest on atrophy of trunk muscles. Eur. J. Appl. Physiol. 112, 43–48.
Inagaki, Y., Madarame, H., Neya, M., Ishii, N., 2011. Increase in serum growth hormone induced by electrical stimulation of muscle combined with blood flow restriction. Eur. J. Appl. Physiol. 111, 2715–2721.
Inder, J.D., Carlson, D.J., Dieberg, G., McFarlane, J.R., Hess, N.C., Smart, N.A., 2016. Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. Hypertens. Res. 39, 88–94.
Izquierdo, M., Ibañez, J., HAkkinen, K., Kraemer, W.J., Larrión, J.L., Gorostiaga, E.M., 2004. Once weekly combined resistance and cardiovascular training in healthy older men. Med. Sci. Sports Exerc. 36, 435–443.
Jaafar, H., 2016. Maximal voluntary co-contraction task: potential utility for individuals in microgravity. Phys. Sportsmed. 44, 240–241.
Jones, S., Man, W.D., Gao, W., Higginson, I.J., Wilcock, A., Maddocks, M., 2016. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. Cochrane Database Syst. Rev. 10, CD009419.
Karabulut, M., Abe, T., Sato, Y., Bemben, M.G., 2010. The effects of low-intensity resistance training with vascular restriction on leg muscle strength in older men. Eur. J. Appl. Physiol. 108, 147–155.
Kawada, S., Ishii, N., 2005. Skeletal muscle hypertrophy after chronic restriction of venous blood flow in rats. Med. Sci. Sports Exerc. 37, 1144–1150.
Kawakami, Y., Akima, H., Kubo, K., Muraoka, Y., Hasegawa, H., Kouzaki, M., Imai, M., Suzuki, Y., Gunji, A., Kanehisa, H., Fukunaga, T., 2001. Changes in muscle size, architecture, and neural activation after 20 days of bed rest with and without resistance exercise. Eur. J. Appl. Physiol. 84, 7–12.
Kern, H., Barberi, L., Löfler, S., Sbardella, S., Burggraf, S., Fruhmann, H., Carraro, U., Mosole, S., Sarabon, N., Vogelauer, M., Mayr, W., Krenn, M., Cvecka, J., Romanello, V., Pietrangelo, L., Protasi, F., Sandri, M., Zampieri, S., Musaro, A., 2014. Electrical stimulation counteracts muscle decline in seniors. Front. Aging Neurosci. 6, 189.
Krol, P., Piecha, M., Slomka, K., Sobota, G., Polak, A., Juras, G., 2011. The effect of whole-body vibration frequency and amplitude on the myoelectric activity of vastus medialis and vastus lateralis. J. Sports Sci. Med. 10, 169–174.
Kubota, A., Sakuraba, K., Sawaki, K., Sumide, T., Tamura, Y., 2008. Prevention of disuse muscular weakness by restriction of blood flow. Med. Sci. Sports Exerc. 40, 529–534.
Kubota, A., Sakuraba, K., Koh, S., Ogura, Y., Tamura, Y., 2011. Blood flow restriction by low compressive force prevents disuse muscular weakness. J. Sci. Med. Sport 14, 95–99.
Lau, R.W., Liao, L.R., Yu, F., Teo, T., Chung, R.C., Pang, M.Y., 2011. The effects of whole body vibration therapy on bone mineral density and leg muscle strength in older adults: a systematic review and meta-analysis. Clin. Rehabil. 25, 975–988.
Lawler, J.M., Song, W., Kwak, H.B., 2006. Differential response of heat shock proteins to hindlimb unloading and reloading in the soleus. Muscle Nerve 33, 200–207.
Lee, S.Y., Im, S.H., Kim, B.R., Choi, J.H., Lee, S.J., Han, E.Y., 2012. The effects of neuromuscular electrical stimulation on cardiopulmonary function in healthy adults. Ann. Rehabil. Med. 36, 849–856.
Loenneke, J.P., Abe, T., Wilson, J.M., Thiebaud, R.S., Fahs, C.A., Rossow, L.M., Bemben, M.G., 2012a. Blood flow restriction: an evidence based progressive model (Review). Acta Physiol. Hung. 99, 235–250.
Loenneke, J.P., Fahs, C.A., Thiebaud, R.S., Rossow, L.M., Abe, T., Ye, X., Kim, D., Bemben, M.G., 2012b. The acute muscle swelling effects of blood flow restriction. Acta Physiol. Hung. 99, 400–410.
Loenneke, J.P., Wilson, J.M., Marín, P.J., Zourdos, M.C., Bemben, M.G., 2012c. Low intensity blood flow restriction training: a meta-analysis. Eur. J. Appl. Physiol. 112, 1849–1859.
Lopez, P., Pinto, R.S., Radaelli, R., Rech, A., Grazioli, R., Izquierdo, M., Cadore, E.L., 2017. Benefits of resistance training in physically frail elderly: a systematic review. Aging Clin. Exp. Res.
Ma, C., Liu, A., Sun, M., Zhu, H., Wu, H., 2016. Effect of whole-body vibration on reduction of bone loss and fall prevention in postmenopausal women: a meta-analysis and systematic review. J. Orthop. Surg. Res. 11, 24.
MacKenzie, S.J., Rannelli, L.A., Yurchevich, J.J., 2010. Neuromuscular adaptations following antagonist resisted training. J. Strength Cond. Res. 24, 156–164.
Maeo, S., Kanehisa, H., 2014. Maximal voluntary Co-contraction training may not always be effective for some leg muscles. J. Sports Sci. Med. 13, 217–218.
Maeo, S., Takahashi, T., Takai, Y., Kanehisa, H., 2013. Trainability of muscular activity level during maximal voluntary co-contraction: comparison between bodybuilders and nonathletes. PLoS One 8, e79486.
Maeo, S., Yoshitake, Y., Takai, Y., Fukunaga, T., Kanehisa, H., 2014a. Effect of short-term maximal voluntary co-contraction training on neuromuscular function. Int. J. Sports Med. 35, 125–134.
Maeo, S., Yoshitake, Y., Takai, Y., Fukunaga, T., Kanehisa, H., 2014b. Neuromuscular adaptations following 12-week maximal voluntary co-contraction training. Eur. J. Appl. Physiol. 114, 663–673.
Maffiuletti, N.A., Pensini, M., Martin, A., 2002. Activation of human plantar flexor muscles increases after electromyostimulation training. J. Appl. Physiol. 92,

1383–1392.
Maffiuletti, N.A., Roig, M., Karatzanos, E., Nanas, S., 2013. Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: a systematic review. BMC Med. 11, 137.
Maffiuletti, N.A., Gondin, J., Place, N., Stevens-Lapsley, J., Vivodtzev, I., Minetto, M.A., 2018. Clinical use of neuromuscular electrical stimulation for neuromuscular rehabilitation: what are we overlooking? Arch. Phys. Med. Rehabil. 99 (4), 806–812.
Maggioni, M.A., Cè, E., Rampichini, S., Ferrario, M., Giordano, G., Veicsteinas, A., Merati, G., 2010. Electrical stimulation versus kinesitherapy in improving functional fitness in older women: a randomized controlled trial. Arch. Gerontol. Geriatr. 50, e19–25.
Mallery, L.H., MacDonald, E.A., Hubley-Kozey, C.L., Earl, M.E., Rockwood, K., MacKnight, C., 2003. The feasibility of performing resistance exercise with acutely ill hospitalized older adults. BMC Geriatr. 3, 3.
Martínez-Velilla, N., Urbistondo-Lasa, G., Veintemilla-Erice, E., Cambra-Contín, K., 2013. [Determining the hours hospitalised patients are bedridden due to their medical condition and functional impairment and secondary mortality]. Rev. Esp. Geriatr. Gerontol. 48, 96.
Martínez-Velilla, N., Cadore, L., Casas-Herrero, Á., Idoate-Saralegui, F., Izquierdo, M., 2016. Physical activity and early rehabilitation in hospitalized elderly medical patients: systematic review of randomized clinical trials. J. Nutr. Health Aging 20, 738–751.
McGuire, D.K., Levine, B.D., Williamson, J.W., Snell, P.G., Blomqvist, C.G., Saltin, B., Mitchell, J.H., 2001. A 30-year follow-up of the Dallas Bedrest and Training Study: I. Effect of age on the cardiovascular response to exercise. Circulation 104, 1350–1357.
Mignardot, J.B., Deschamps, T., Le Goff, C.G., Roumier, F.X., Duclay, J., Martin, A., Sixt, M., Pousson, M., Cornu, C., 2015. Neuromuscular electrical stimulation leads to physiological gains enhancing postural balance in the pre-frail elderly. Physiol. Rep. 3.
Miokovic, T., Armbrecht, G., Gast, U., Rawer, R., Roth, H.J., Runge, M., Felsenberg, D., Belavý, D.L., 2014. Muscle atrophy, pain, and damage in bed rest reduced by resistive (vibration) exercise. Med. Sci. Sports Exerc. 46, 1506–1516.
Morse, C.I., Thom, J.M., Mian, O.S., Muirhead, A., Birch, K.M., Narici, M.V., 2005. Muscle strength, volume and activation following 12-month resistance training in 70-year-old males. Eur. J. Appl. Physiol. 95, 197–204.
Motalebi, S.A., Cheong, L.S., Iranagh, J.A., Mohammadi, F., 2018. Effect of low-cost resistance training on lower-limb strength and balance in institutionalized seniors. Exp. Aging Res. 44, 48–61.
Nelson, M.E., Rejeski, W.J., Blair, S.N., Duncan, P.W., Judge, J.O., King, A.C., Macera, C.A., Castaneda-Sceppa, C., Medicine, A.Co.S., Association, A.H., 2007. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation 116, 1094–1105.
Nordlund, M.M., Thorstensson, A., 2007. Strength training effects of whole-body vibration? Scand. J. Med. Sci. Sports 17, 12–17.
Oliveira, L.C., Oliveira, R.G., Pires-Oliveira, D.A., 2016. Effects of whole body vibration on bone mineral density in postmenopausal women: a systematic review and meta-analysis. Osteoporos. Int. 27, 2913–2933.
Ozaki, H., Miyachi, M., Nakajima, T., Abe, T., 2011. Effects of 10 weeks walk training with leg blood flow reduction on carotid arterial compliance and muscle size in the elderly adults. Angiology 62, 81–86.
Paillard, T., 2018. Muscle plasticity of aged subjects in response to electrical stimulation training and inversion and/or limitation of the sarcopenic process. Ageing Res. Rev. (46), 1–13 published in May in ARR.
Paillard, T., Noé, F., Passelergue, P., Dupui, P., 2005. Electrical stimulation superimposed onto voluntary muscular contraction. Sports Med. 35, 951–966.
Pedersen, M.M., Bodilsen, A.C., Petersen, J., Beyer, N., Andersen, O., Lawson-Smith, L., Kehlet, H., Bandholm, T., 2013. Twenty-four-hour mobility during acute hospitalization in older medical patients. J. Gerontol. A Biol. Sci. Med. Sci. 68, 331–337.
Pellegrino, M.A., Desaphy, J.F., Brocca, L., Pierno, S., Camerino, D.C., Bottinelli, R., 2011. Redox homeostasis, oxidative stress and disuse muscle atrophy. J. Physiol. 589, 2147–2160.
Phillips, S.M., Glover, E.I., Rennie, M.J., 2009. Alterations of protein turnover underlying disuse atrophy in human skeletal muscle. J. Appl. Physiol. 107, 645–654.
Pietrangelo, T., Mancinelli, R., Toniolo, L., Cancellara, L., Paoli, A., Puglielli, C., Iodice, P., Doria, C., Bosco, G., D'Amelio, L., di Tano, G., Fulle, S., Saggini, R., Fanò, G., Reggiani, C., 2009. Effects of local vibrations on skeletal muscle trophism in elderly people: mechanical, cellular, and molecular events. Int. J. Mol. Med. 24, 503–512.
Pišot, R., Marusic, U., Biolo, G., Mazzucco, S., Lazzer, S., Grassi, B., Reggiani, C., Toniolo, L., di Prampero, P.E., Passaro, A., Narici, M., Mohammed, S., Rittweger, J., Gasparini, M., Gabrijelčič Blenkuš, M., Šimunič, B., 2016. Greater loss in muscle mass and function but smaller metabolic alterations in older compared with younger men following 2 wk of bed rest and recovery. J. Appl. Physiol. 120, 922–929.
Powers, S.K., Talbert, E.E., Adhihetty, P.J., 2011. Reactive oxygen and nitrogen species as intracellular signals in skeletal muscle. J. Physiol. 589, 2129–2138.
Powers, S.K., Wiggs, M.P., Duarte, J.A., Zergeroglu, A.M., Demirel, H.A., 2012. Mitochondrial signaling contributes to disuse muscle atrophy. Am. J. Physiol. Endocrinol. Metab. 303, E31–E39.
Ramírez-Campillo, R., Castillo, A., de la Fuente, C.I., Campos-Jara, C., Andrade, D.C., Álvarez, C., Martínez, C., Castro-Sepúlveda, M., Pereira, A., Marques, M.C., Izquierdo, M., 2014. High-speed resistance training is more effective than low-speed resistance training to increase functional capacity and muscle performance in older women. Exp. Gerontol. 58, 51–57.
Reeves, N.D., Narici, M.V., Maganaris, C.N., 2004. In vivo human muscle structure and function: adaptations to resistance training in old age. Exp. Physiol. 89, 675–689.
Reeves, N.D., Narici, M.V., Maganaris, C.N., 2006. Myotendinous plasticity to ageing and resistance exercise in humans. Exp. Physiol. 91, 483–498.
Reid, K.F., Fielding, R.A., 2012. Skeletal muscle power: a critical determinant of physical functioning in older adults. Exerc. Sport Sci. Rev. 40, 4–12.
Rittweger, J., 2010. Vibration as an exercise modality: how it may work, and what its potential might be. Eur. J. Appl. Physiol. 108, 877–904.
Robinson, S.M., Reginster, J.Y., Rizzoli, R., Shaw, S.C., Kanis, J.A., Bautmans, I., Bischoff-Ferrari, H., Bruyère, O., Cesari, M., Dawson-Hughes, B., Fielding, R.A., Kaufman, J.M., Landi, F., Malafarina, V., Rolland, Y., van Loon, L.J., Vellas, B., Visser, M., Cooper, C., Group, Ew., 2017. Does nutrition play a role in the prevention and management of sarcopenia? Clin. Nutr. 37 (4), 1121–1132.
Rodriguez-Mañas, L., Fried, L.P., 2015. Frailty in the clinical scenario. Lancet 385, e7–e9.
Rogan, S., Taeymans, J., Radlinger, L., Naepflin, S., Ruppen, S., Bruelhart, Y., Hilfiker, R., 2017. Effects of whole-body vibration on postural control in elderly: an update of a systematic review and meta-analysis. Arch. Gerontol. Geriatr. 73, 95–112.
Rubin, C., Turner, A.S., Bain, S., Mallinckrodt, C., McLeod, K., 2001. Anabolism. Low mechanical signals strengthen long bones. Nature 412, 603–604.
Ruiz, J.R., Sui, X., Lobelo, F., Morrow, J.R., Jackson, A.W., Sjöström, M., Blair, S.N., 2008. Association between muscular strength and mortality in men: prospective cohort study. BMJ 337, a439.
Ryan, T.E., Erickson, M.L., Young, H.J., McCully, K.K., 2013. Case report: endurance electrical stimulation training improves skeletal muscle oxidative capacity in chronic spinal cord injury. Arch. Phys. Med. Rehabil. 94, 2559–2561.
Schoenfeld, B.J., 2013. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. Sports Med. 43, 179–194.
Scott, B.R., Loenneke, J.P., Slattery, K.M., Dascombe, B.J., 2015. Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. Sports Med. 45, 313–325.
Senf, S.M., Dodd, S.L., McClung, J.M., Judge, A.R., 2008. Hsp70 overexpression inhibits NF-kappaB and Foxo3a transcriptional activities and prevents skeletal muscle atrophy. FASEB J. 22, 3836–3845.
Serra-Rexach, J.A., Bustamante-Ara, N., Hierro Villarán, M., González Gil, P., Sanz Ibáñez, M.J., Blanco Sanz, N., Ortega Santamaría, V., Gutiérrez Sanz, N., Marín Prada, A.B., Gallardo, C., Rodríguez Romo, G., Ruiz, J.R., Lucia, A., 2011. Short-term, light- to moderate-intensity exercise training improves leg muscle strength in the oldest old: a randomized controlled trial. J. Am. Geriatr. Soc. 59, 594–602.
Serrau, V., Driss, T., Vandewalle, H., Behm, D.G., Lesne-Chabran, E., Le Pellec-Muller, A., 2012. Muscle activation of the elbow flexor and extensor muscles during self-resistance exercises: comparison of unilateral maximal cocontraction and bilateral self-resistance. J. Strength Cond. Res. 26, 2468–2477.
Shackelford, L.C., LeBlanc, A.D., Driscoll, T.B., Evans, H.J., Rianon, N.J., Smith, S.M., Spector, E., Feeback, D.L., Lai, D., 2004. Resistance exercise as a countermeasure to disuse-induced bone loss. J. Appl. Physiol. 97, 119–129.
Shad, B.J., Thompson, J.L., Breen, L., 2016. Does the muscle protein synthetic response to exercise and amino acid-based nutrition diminish with advancing age? A systematic review. Am. J. Physiol. Endocrinol. Metab. 311, E803–E817.
Sitjà-Rabert, M., Rigau, D., Fort Vanmeerghaeghe, A., Romero-Rodríguez, D., Bonastre Subirana, M., Bonfill, X., 2012. Efficacy of whole body vibration exercise in older people: a systematic review. Disabil. Rehabil. 34, 883–893.
Slysz, J., Stultz, J., Burr, J.F., 2016. The efficacy of blood flow restricted exercise: a systematic review & meta-analysis. J. Sci. Med. Sport 19, 669–675.
Srikanthan, P., Karlamangla, A.S., 2014. Muscle mass index as a predictor of longevity in older adults. Am. J. Med. 127, 547–553.
Steib, S., Schoene, D., Pfeifer, K., 2010. Dose-response relationship of resistance training in older adults: a meta-analysis. Med. Sci. Sports Exerc. 42, 902–914.
Straight, C.R., Lindheimer, J.B., Brady, A.O., Dishman, R.K., Evans, E.M., 2016. Effects of resistance training on lower-extremity muscle power in middle-aged and older adults: a systematic review and meta-analysis of randomized controlled trials. Sports Med. 46, 353–364.
Suetta, C., Magnusson, S.P., Rosted, A., Aagaard, P., Jakobsen, A.K., Larsen, L.H., Duus, B., Kjaer, M., 2004. Resistance training in the early postoperative phase reduces hospitalization and leads to muscle hypertrophy in elderly hip surgery patients–a controlled, randomized study. J. Am. Geriatr. Soc. 52, 2016–2022.
Suetta, C., Andersen, J.L., Dalgas, U., Berget, J., Koskinen, S., Aagaard, P., Magnusson, S.P., Kjaer, M., 2008. Resistance training induces qualitative changes in muscle morphology, muscle architecture, and muscle function in elderly postoperative patients. J. Appl. Physiol. 105, 180–186.
Suetta, C., Frandsen, U., Mackey, A.L., Jensen, L., Hvid, L.G., Bayer, M.L., Petersson, S.J., Schrøder, H.D., Andersen, J.L., Aagaard, P., Schjerling, P., Kjaer, M., 2013. Ageing is associated with diminished muscle re-growth and myogenic precursor cell expansion early after immobility-induced atrophy in human skeletal muscle. J. Physiol. 591, 3789–3804.
Takano, H., Morita, T., Iida, H., Asada, K., Kato, M., Uno, K., Hirose, K., Matsumoto, A., Takenaka, K., Hirata, Y., Eto, F., Nagai, R., Sato, Y., Nakajima, T., 2005. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. Eur. J. Appl. Physiol. 95, 65–73.
Takarada, Y., Takazawa, H., Ishii, N., 2000. Applications of vascular occlusion diminish disuse atrophy of knee extensor muscles. Med. Sci. Sports Exerc. 32, 2035–2039.
Tanner, R.E., Brunker, L.B., Agergaard, J., Barrows, K.M., Briggs, R.A., Kwon, O.S., Young, L.M., Hopkins, P.N., Volpi, E., Marcus, R.L., LaStayo, P.C., Drummond, M.J., 2015. Age-related differences in lean mass, protein synthesis and skeletal muscle markers of proteolysis after bed rest and exercise rehabilitation. J. Physiol. 593, 4259–4273.
Taradaj, J., Halski, T., Kucharzewski, M., Walewicz, K., Smykla, A., Ozon, M., Slupska, L., Dymarek, R., Ptaszkowski, K., Rajfur, J., Pasternok, M., 2013. The effect of neuromuscular electrical stimulation on quadriceps strength and knee function in professional soccer players: return to sport after ACL reconstruction. Biomed Res. Int., 802534.
Tschopp, M., Sattelmayer, M.K., Hilfiker, R., 2011. Is power training or conventional

resistance training better for function in elderly persons? A meta-analysis. Age Ageing 40, 549–556.
Vaquero, A.F., Chicharro, J.L., Gil, L., Ruiz, M.P., Sánchez, V., Lucía, A., Urrea, S., Gómez, M.A., 1998. Effects of muscle electrical stimulation on peak VO2 in cardiac transplant patients. Int. J. Sports Med. 19, 317–322.
Vechin, F.C., Libardi, C.A., Conceição, M.S., Damas, F.R., Lixandrão, M.E., Berton, R.P., Tricoli, V.A., Roschel, H.A., Cavaglieri, C.R., Chacon-Mikahil, M.P., Ugrinowitsch, C., 2015. Comparisons between low-intensity resistance training with blood flow restriction and high-intensity resistance training on quadriceps muscle mass and strength in elderly. J. Strength Cond. Res. 29, 1071–1076.
Veldman, M.P., Gondin, J., Place, N., Maffiuletti, N.A., 2016. Effects of neuromuscular electrical stimulation training on endurance performance. Front. Physiol. 7, 544.
Vigelsø, A., Gram, M., Wiuff, C., Andersen, J.L., Helge, J.W., Dela, F., 2015. Six weeks' aerobic retraining after two weeks' immobilization restores leg lean mass and aerobic capacity but does not fully rehabilitate leg strength in young and older men. J. Rehabil. Med. 47, 552–560.
Villumsen, M., Jorgensen, M.G., Andreasen, J., Rathleff, M.S., Mølgaard, C.M., 2015. Very low levels of physical activity in older patients during hospitalization at an acute geriatric ward: a prospective cohort study. J. Aging Phys. Act. 23, 542–549.
Vinstrup, J., Skals, S., Calatayud, J., Jakobsen, M.D., Sundstrup, E., Pinto, M.D., Izquierdo, M., Wang, Y., Zebis, M.K., Andersen, L.L., 2017. Electromyographic evaluation of high-intensity elastic resistance exercises for lower extremity muscles during bed rest. Eur. J. Appl. Physiol. 117, 1329–1338.
von Haehling, S., Morley, J.E., Anker, S.D., 2010. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. J. Cachexia Sarcopenia Muscle 1, 129–133.
Wall, B.T., van Loon, L.J., 2013. Nutritional strategies to attenuate muscle disuse atrophy. Nutr. Rev. 71, 195–208.
Wall, B.T., Dirks, M.L., van Loon, L.J., 2013. Skeletal muscle atrophy during short-term disuse: implications for age-related sarcopenia. Ageing Res. Rev. 12, 898–906.
Watenpaugh, D.E., Ballard, R.E., Schneider, S.M., Lee, S.M., Ertl, A.C., William, J.M., Boda, W.L., Hutchinson, K.J., Hargens, A.R., 2000. Supine lower body negative pressure exercise during bed rest maintains upright exercise capacity. J. Appl. Physiol. 89, 218–227.
Wernbom, M., Apro, W., Paulsen, G., Nilsen, T.S., Blomstrand, E., Raastad, T., 2013. Acute low-load resistance exercise with and without blood flow restriction increased protein signalling and number of satellite cells in human skeletal muscle. Eur. J. Appl. Physiol. 113, 2953–2965.
Wiggs, M.P., 2015. Can endurance exercise preconditioning prevention disuse muscle atrophy? Front. Physiol. 6, 63.
Wilson, J.M., Lowery, R.P., Joy, J.M., Loenneke, J.P., Naimo, M.A., 2013. Practical blood flow restriction training increases acute determinants of hypertrophy without increasing indices of muscle damage. J. Strength Cond. Res. 27, 3068–3075.
Wollersheim, T., Haas, K., Wolf, S., Mai, K., Spies, C., Steinhagen-Thiessen, E., Wernecke, K.D., Spranger, J., Weber-Carstens, S., 2017. Whole-body vibration to prevent intensive care unit-acquired weakness: safety, feasibility, and metabolic response. Crit Care 21, 9.
Yasuda, T., Fukumura, K., Fukuda, T., Uchida, Y., Iida, H., Meguro, M., Sato, Y., Yamasoba, T., Nakajima, T., 2014. Muscle size and arterial stiffness after blood flow-restricted low-intensity resistance training in older adults. Scand. J. Med. Sci. Sports 24, 799–806.
Zanchi, N.E., Lancha, A.H., 2008. Mechanical stimuli of skeletal muscle: implications on mTOR/p70s6k and protein synthesis. Eur. J. Appl. Physiol. 102, 253–263.
Zisberg, A., Shadmi, E., Sinoff, G., Gur-Yaish, N., Srulovici, E., Admi, H., 2011. Low mobility during hospitalization and functional decline in older adults. J. Am. Geriatr. Soc. 59, 266–273.

Effect of exercise on hospitalization-associated disability in older patients

With the aim of assessing the effects of an inhospital exercise programs in older adults hospitalized with an acute medical condition, we performed a randomized controlled trial that was published in *The Journal of American Medical Directors Association* (impact factor: 4.899, position 6/53, category: Geriatrics).[55] Our findings show that a simple exercise program solely consisting of walking and rising from a chair is safe and can reduce the risk of HAD in hospitalized older adults. A graphical abstract of this trial is shown in Figure 4.

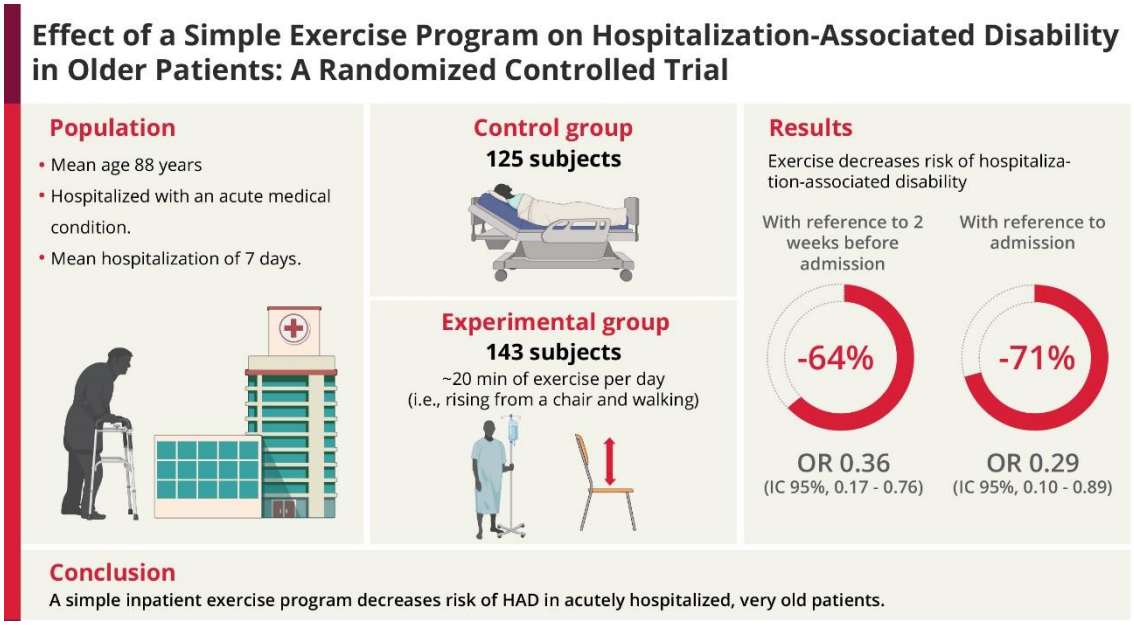


Figure 4. Summary of the effects of inhospital exercise in acutely hospitalized older adults.

JAMDA xxx (2019) 1–7

JAMDA

journal homepage: www.jamda.com

Original Study

Effect of a Simple Exercise Program on Hospitalization-Associated Disability in Older Patients: A Randomized Controlled Trial

Javier Ortiz-Alonso MD [a,b,c,*,†], Natalia Bustamante-Ara PhD [d,†], Pedro L. Valenzuela MSc [e,†], Maite Vidán-Astiz MD, PhD [a,b,c,f], Gabriel Rodríguez-Romo PhD [c,g], Jennifer Mayordomo-Cava PhD [b,c], Marianna Javier-González MD [a], Mercedes Hidalgo-Gamarra MD [a], Myriel Lopéz-Tatis MD [a], María Isabel Valades-Malagón BSN [a], Alejandro Santos-Lozano PhD [h,i], Alejandro Lucia MD, PhD [c,i,j], José Antonio Serra-Rexach MD, PhD [a,b,c,f]

[a] *Geriatric Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[b] *Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain*
[c] *Biomedical Research Networking Center on Frailty and Healthy Aging, CIBERFES, Madrid, Spain*
[d] *Universidad Autónoma de Chile, Talca, Chile*
[e] *Systems Biology Department, University of Alcalá, Madrid, Spain*
[f] *School of Medicine, Universidad Complutense, Madrid, Spain*
[g] *Sports Department, Instituto Nacional de Educación Física, Universidad Politécnica, Madrid, Spain*
[h] *i+HeALTH, European University Miguel de Cervantes, Valladolid, Spain*
[i] *Research Institute Hospital 12 de Octubre ('i+12'), Madrid, Spain*
[j] *Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain*

Keywords:
Activities of daily living
functional decline
physical activity
geriatric assessment
hospitalization
intervention

A B S T R A C T

Objective: Hospitalization-associated disability [HAD, ie, the loss of ability to perform ≥1 basic activities of daily living (ADLs) independently at discharge] is a frequent condition among older patients. The present study assessed whether a simple inpatient exercise program decreases HAD incidence in acutely hospitalized very old patients.

Design: In this randomized controlled trial (Activity in Geriatric Acute Care) participants were assigned to a control or intervention group and were assessed at baseline, admission, discharge, and 3 months thereafter.

Setting and Participants: In total, 268 patients (mean age 88 years, range 75–102) admitted to an acute care for older patients unit of a public hospital were randomized to a control (n = 125) or intervention (exercise) group (n = 143).

Methods: Both groups received usual care, and patients in the intervention group also performed simple supervised exercises (walking and rising from a chair, for a total duration of ~20 minutes/day). We measured ADL function (Katz index) and incident HAD at discharge and after 3 months (primary outcome) and Short Physical Performance Battery, ambulatory capacity, number of falls, rehospitalization, and death during a 3-month follow-up (secondary outcomes).

Results: Median duration of hospitalization was 7 days (interquartile range 4 days). The intervention group had a lower risk of HAD with reference to both baseline [odds ratio (OR) 0.36; 95% confidence interval (CI) 0.17–0.76, $P = .007$] and admission (OR 0.29; 95% CI 0.10–0.89, $P = .030$). A trend toward an

This study was supported by the Instituto de Salud Carlos III (Ministerio de Ciencia, Innovación y Universidades, Spain) (RD12/0043/0025, PI12/02852, PI15/00558 and PI18/00139); Biomedical Research Networking Center on Frailty and Healthy Aging (CIBERFES, Spain); and FEDER funds from the European Union. The work of Pedro L. Valenzuela is supported by a contract granted by the University of Alcalá (FPI2016).

The authors declare no conflicts of interest.

Trial registration: NCT0137489 (https://clinicaltrials.gov/ct2/show/NCT01374893).

* Address correspondence to Javier Ortiz-Alonso, MD, Geriatric Service, Hospital General Universitario Gregorio Marañón, Calle Doctor Esquerdo, no.46, Madrid 28007, Spain.

E-mail address: javier.ortiz@salud.madrid.org (J. Ortiz-Alonso).

† These authors contributed equally to this work.

https://doi.org/10.1016/j.jamda.2019.11.027

improved ADL function at discharge vs admission was found in the intervention group compared with controls (OR 0.32; 95% CI –0.04 to 0.68; $P = .083$). No between-group differences were noted for the other endpoints (all $P > .05$).

Conclusion and Implications: A simple inpatient exercise program decreases risk of HAD in acutely hospitalized, very old patients.

Hospitalization-associated disability [HAD, ie, loss of the ability to perform one or more basic activities of daily living (ADLs) independently at discharge] occurs in more than one-third of hospitalized older adults.[1–4] This condition is associated with long-term disability, institutionalization, and death,[5–7] and therefore its prevention should be a priority.

Hospitalized older patients spend most of the time in bed, even if they are able to walk independently,[8] and the majority (73%) do not walk at all during hospitalization.[9] Several physical strategies can be applied to prevent the functional decline associated with periods of restricted mobility such as those imposed by hospitalization, but physical exercise appears to be the most effective.[10,11] Exercise interventions have proven feasible and safe in acutely hospitalized older medical patients and are effective to improve their functional status at discharge as well as to reduce the length and cost of hospital stays.[12–14] It has been recommended that hospitalized older people should perform multicomponent exercise programs, ie, combining walking and resistance exercises.[12] However, this type of intervention usually involves complex exercises and requires the purchase of weight-training equipment, which might hinder its routine implementation in some acute care of older patient (ACE) units.

The aim of this study was to determine the effects of an inpatient exercise program including simple physical exercises for patients admitted to an ACE unit on ability to perform ADLs independently (herein, ADL function) and incident HAD at discharge and at 3 months postdischarge (primary endpoints) as well as performance on the Short Physical Performance Battery (SPPB), independent-walking ability [functional ambulatory classification (FAC)], and number of falls, rehospitalization, and mortality risk during the 3 months following discharge (secondary endpoints).

Methods

Study Design

This clinical trial (NCT01374893) complied with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement.[15] Patients (>75 years) admitted to our ACE unit from June 2012 to June 2014 were considered eligible to participate in the study. During these 2 years, the patients were eligible to be included in the control or intervention group in a time-dependent manner (ie, using 4- or 8-week blocks), to avoid the co-presence of patients from both groups in the unit, such that the patients were blinded to actual group assignment. We then excluded those who were nonambulatory or dependent in all basic ADLs at baseline (ie, 2 weeks before admission, as assessed by retrospective interview), had unstable cardiovascular disease or any other major medical condition contraindicating exercise, terminal illness, severe dementia [ie, ≥8 errors in the Spanish version of the short portable mental status questionnaire (SPMSQ), also known as the Pfeiffer test],[16] an expected length of hospitalization <3 days, were transferred from another hospital unit, or had a scheduled admission (which was usually associated with a length of hospitalization <3 days). Only those hospitalized for 3 or more days and alive at discharge were included. The Institutional Review Board approved the protocol, and written informed consent was obtained from patients. When it was not possible to obtain the informed consent directly from a patient because of medical reasons (eg, impaired cognitive function), proxy consent was obtained from their relatives. All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Both groups received standard care in our ACE unit.[17]

Intervention

The intervention started the day after admission, was performed on weekdays and included 1 to 3 sessions per day (total duration, ~ 20 minutes/day). It consisted solely of rising from a seated to an upright position (using armrests/assistance if necessary) in the patient's room and supervised walking exercises along the corridor of the ward. Standing and walking exercises were separated by a rest period of up to 5 minutes. A detailed description of the exercises is shown in Table 1, and representative examples are available as Supplementary Video 1 and Supplementary Video 2. All the exercise sessions were supervised by a fitness specialist (N.A. or G.R.), and training loads were recorded in a notebook.

Endpoints

The research staff included nurses, medical residents, and the aforementioned fitness specialists, who were in charge of supervising each session. Those involved in outcome assessment were not involved in supervising the intervention. However, assessors and care providers were not blinded to the assigned intervention.

ADL function and FAC at baseline (ie, 2 weeks before admission) were assessed in a retrospective interview. Together with SPPB, ADL function and FAC were also assessed at admission and discharge. Finally, ADL function and FAC, as well as mortality and number of falls during the 3-month follow-up, were assessed by telephone interview at 3 months postdischarge.

ADL function was assessed using the Katz index of independence in ADL, which includes 6 ADLs (eating, transferring from bed to chair, walking, using the toilet, bathing, and dressing), each of which is scored with 0 or 1 depending on whether the participant is able to perform the activity with or without help, respectively.[18] Then, the 6 individual items are summed, resulting in a total 0 to 6 score. HAD was considered as a dichotomous variable attending to whether the patient had lost or not the ability to perform 1 or more ADLs independently, and was assessed at discharge and 3 months later.[1]

Ambulatory capacity was assessed using the modified FAC, which classifies patients in 5 different categories attending to their level of dependence during walking; a score of 0 was assigned if the patient cannot walk, 1 if the patient requires continuous manual contact to support the body, 2 for light or intermittent manual contact to assist balance, 3 for independent but supervised ambulation, and 4 for independent ambulation on level surfaces or stairs.[19] The modified FAC has demonstrated good reliability and validity in older people (eg, patients with hip fracture[20] or stroke patients[21,22]). We also assessed the loss of independent, nonsupervised ambulation (ie, FAC score <4)[19] at discharge and 3 months later.

Table 1
Exercise Intervention (Total Duration ~20 Minutes/Day)

Exercise Modality	Description	Dose
Sit-to-stand	Supervised rising from a seated to an upright position, using assistance (armrest of an external person) if needed.	• Frequency: 1 to a maximum of 3 sessions/d, only during weekdays (starting with 1 session and with number of sessions gradually increasing depending on the patient's physical capacity); 30-min rest between consecutive sessions. • Volume: from 1 to a maximum of 3 sets (depending on the patients' physical capacity) of up to a maximum of 10 repetitions for each session; 2-min rest between sets.
Walking	Supervised walking on the corridor, using assistance (mobility aids such as walkers, or an external person) if needed.	• Frequency: Same as above. • Volume: from 3 to a maximum of 10 min (depending on the patient's physical capacity) per session, with resting periods if needed.

The SPPB, which has shown to validly assess lower extremity function in older persons across a broad spectrum of function levels,[23] was assessed as a marker of physical performance capacity. The SPPB measures performance in 3 different tests (repeated chair stand test, time needed to walk a distance of 4 meters 2 times, and a hierarchical standing balance test), which are scored from 0 to 4, with a 0-to-12 sum-score for all 3 tests combined.[23]

Although the original protocol specified a change in SPPB score as the primary endpoint,[15] an interim analysis after 4 months revealed that 94% (intervention) and 84% (controls) of patients had an SPPB score <6 on a 0–12 scale, masking a potential intervention effect. Accordingly, we considered that the intervention effects would not be noticeable in a test such as the SPPB given the very low physical performance capacity of the study participants, whereas ability to perform basic ADLs might be more responsive to the intervention in this patient group. Thus, HAD was established as the primary endpoint.

Statistical Analysis

Prior (unpublished) data obtained in 604 patients showed that 33% of the patients admitted to our ACE unit improved in 1 or more ADLs from admission to discharge. As we hoped to increase this rate by 15% with the intervention (up to 48%), we estimated a sample of 260 or

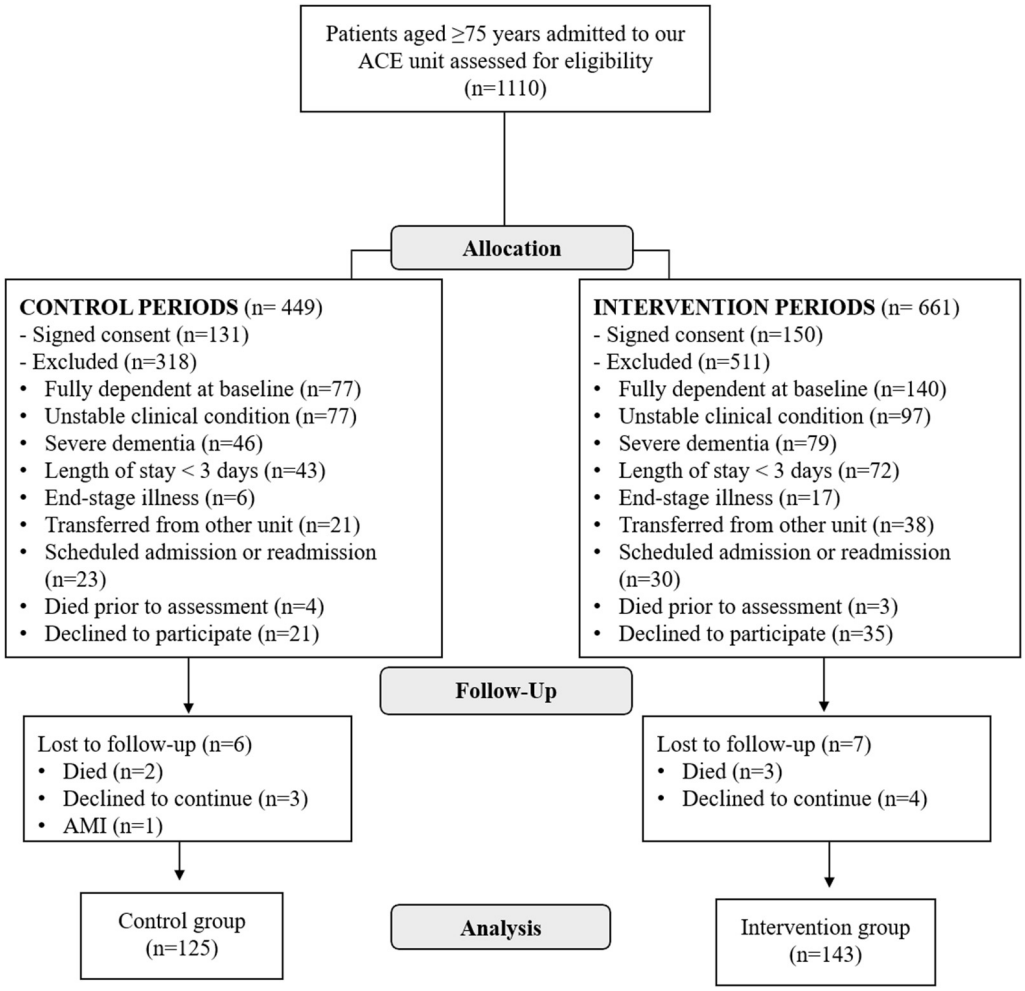


Fig. 1. Flowchart of study participants. AMI, acute myocardial infarction.

more patients to detect a significant intervention effect on incident HAD (power = 80%, $\alpha = 0.05$).

Data are presented as means ± standard deviation. Normal distribution (Shapiro-Wilk test) and homoscedasticity (Levene test) of the data were checked before any statistical treatment. Groups were compared at both baseline and admission using Student independent *t* tests or χ^2 tests for continuous or dichotomous variables, respectively. Between-group differences in continuous endpoint measures were assessed by comparing the intra-individual score differences from baseline/admission to discharge in the 2 groups. Analysis of covariance was used for comparing the mean intra-individual differences in continuous endpoint measures between the 2 groups, with adjustment by baseline/admission values in order to control for imbalances.[24] Between- and within-group differences in nonparametric endpoint measures were analyzed using the Mann-Whitney *U* test and the Wilcoxon signed-rank test, respectively. Binary logistic regression was used to compare the risk of HAD, independent ambulation, rehospitalization, and death between groups. Survival analysis (crude and adjusted Kaplan-Meier) was performed during the 3-month follow-up. Incidence rate ratio (calculated with negative binomial regression) was used to compare the number of falls between groups. We did not impute missing data and, thus, only available data was used for analysis for each specific variable. All statistical analyses were conducted using a statistical software package (SPSS 23.0, IBM, NY) with $\alpha = 0.05$.

Results

A flow diagram of study participants is shown in Figure 1. From a total of 1110 patients admitted to our ACE unit during the study period, 281 met all inclusion criteria and volunteered to participate. Of these, 131 and 150 were assigned to the control and the intervention group, respectively. Finally, 268 patients (n = 125 and 143 for control and intervention, respectively) completed the study and could be included in the analysis. No between-group differences were found at the start of the study for most sociodemographic/clinical variables, but the intervention group presented with a higher incidence of dementia and fall history, and these patients were overall more dependent in ADL function at baseline and admission (Table 2).

The median length of hospitalization was 7 days [interquartile range (IQR) 4], with no between-group differences ($P = .246$). Participants in the intervention group performed a median of 3 training days (IQR 2) and 2 training sessions per day (IQR 2), with an average total exercise time per day of ~20 minutes [for each session, the median duration of the walking part was 5 minutes (IQR 4, range 0 to 10), and patients performed a mean of 9 (standard deviation 6, range 0 to 30) sit-to-stands]. No adverse effects or falls were recorded during the intervention. Five (3.5%) patients did not exercise because they had a rapid, severe functional decline shortly after admission.

The effects of the exercise intervention on ADL function, SPPB, and FAC are shown in Table 3. A decline in ADL function from baseline to both discharge and 3 months later was observed in the 2 groups ($P < .001$), with no significant between-group differences. Yet, in adjusted analyses, only the intervention group significantly improved ADL function from admission to both discharge and 3 months postdischarge ($P < .001$), with a quasi-significant ($P = .083$) difference between groups for the change from admission to discharge. Results for each specific ADL are shown in Supplementary Table 1. No between-group differences were noted for the changes in FAC or SPPB score. However, only the intervention group significantly improved the SPPB score from admission to discharge ($P = .013$). Results for each specific test of the SPPB are shown in Supplementary Table 2.

Compared with controls, patients in the intervention group had a significantly lower incidence of HAD at discharge with reference to both baseline and admission, even when adjusting for clinical characteristics and functional performance at admission (Table 4). No between-group differences were found in HAD measured at 3 months postdischarge in adjusted analyses, although there was a trend ($P = .058$) toward a lower incidence of HAD with reference to baseline in the intervention group. The proportion of patients diagnosed with HAD with reference to admission was significantly lower in the intervention group at discharge and 3 months postdischarge ($P = .012$ and .046, respectively). The proportion of patients with HAD with reference to baseline did also differ between groups at discharge ($P = .034$), but not 3 months later ($P = .114$). Also, no intervention effect was noted for risk of rehospitalization or number of falls during the 3-month follow-up (Table 4). A nonsignificant trend toward a lower mortality risk was observed in the intervention group (Table 4), with crude and adjusted Kaplan-Meier analysis confirming this trend ($P = .084$ and .085, respectively).

Table 2
Main Characteristics by Group

Variables	Control (n = 125)	Intervention (n = 143)	*P* value
Age (mean ± SD), y	88 ± 5	88 ± 5	.88
Women	54%	60%	.28
Body mass index (mean ± SD), kg/m^2	26.0 ± 6.4	26.1 ± 9.3	.95
Living at home	93%	91%	.57
Charlson comorbidity index (mean ± SD)	6.8 ± 1.9	6.7 ± 1.7	.88
Geriatric syndromes			
Dementia	12%	27%	**.003**
Depression	18%	32%	**.010**
Falls	16%	36%	**<.001**
Chronic pain	30%	35%	.43
Malnutrition	14%	22%	.085
Urinary incontinence	39%	49%	.11
Frailty phenotype*	65%	74%	.097
Incident delirium	18%	28%	.81
Polypharmacy (≥7)	55%	58%	.64
Main admission diagnosis			.39
Respiratory	26%	34%	
Circulatory	30%	26%	
Renal/urologic	15%	8%	
Central nervous system	7%	13%	
Digestive	7%	8%	
ADL function at baseline (mean ± SD)	4.6 ± 1.7	4.0 ± 1.8	**.012**
FAC at baseline (median, IQR)	4 (0)	4 (1)	.15
Independent ambulation at baseline†	76%	68%	.14
ADL function at admission (mean ± SD)	3.1 ± 2.0	2.3 ± 2.0	**<.001**
FAC at admission (median, IQR)	3 (2)	2 (3)	.14
Independent ambulation at admission†	40%	31%	.13
SPPB (mean ± SD) score at admission	3.8 ± 2.9	3.2 ± 2.5	.078
Length of hospitalization (median [IQR]), d	7 (5)	6 (4)	.25

SD, standard deviation.
Significant differences between groups ($P < .05$) are in bold.
Baseline data corresponded to 2 weeks before admission, as assessed by retrospective interview. ADL function was assessed with the Katz index of independence in ADLs, which uses a total 0 to 6 score and includes the following 6 basic ADLs: bathing, dressing, transferring, toileting, continence, and feeding.
*Frailty was defined as having ≥3 of 5 Fried criteria.[25]
†Independent ambulation was considered in the event of a FAC = 4.[19]

Discussion

The present study shows that performing simple inpatient exercises (walking and rising from a chair) considerably decreases (by ~70%) the risk of HAD in acutely hospitalized frail, very old patients and tends to improve their functional ability. HAD is a frequent condition among hospitalized older adults. Indeed, in our study, 58% and 21% of the patients in the control group suffered HAD at discharge with reference to baseline and admission, respectively. Because HAD

Table 3
Effects of the Exercise Intervention on the Change in ADL Function, Ambulatory Capacity, and Physical Performance Capacity

Median/Mean Change	Control Group	Intervention Group	Unadjusted Difference Between Groups Mean (95% CI)	Adjusted Difference* Between Groups Mean (95% CI)
ADL function (Katz index)				
From baseline to discharge, mean (SD)	–1.26 (1.72)†	–1.03 (1.96)†	0.23 (−0.22, 0.68) $P = .316$	0.03 (−0.40, 0.45) $P = .905$
From admission to discharge, mean (SD)	0.17 (1.61)	0.73 (1.52)†	0.56 (0.18, 0.94) $P = \mathbf{.004}$	0.32 (−0.04, 0.68) $P = .083$
From baseline to 3 mo postdischarge, mean (SD)	–1.31 (1.86)†	–0.85 (1.92)†	0.46 (−0.05, 0.96) $P = .074$	0.27 (−0.21, 0.76) $P = .265$
From admission to 3 mo postdischarge, mean (SD)	0.17 (2.03)	0.88 (1.89)†	0.71 (0.19, 1.23) $P = \mathbf{.007}$	0.39 (−0.09, 0.87) $P = .114$
FAC				
From baseline to discharge, median (IQR)	0 (2)	0 (1)	0.04 (−0.23, 0.31) $P = .556$	-
From admission to discharge, median (IQR)	0 (1)	0 (1)	0.11 (−0.16, 0.39) $P = .153$	-
From baseline to 3 mo postdischarge, median, (IQR)	0 (1)	0 (1)	–0.09 (−0.44, 0.27) $P = .130$	-
From admission to 3 mo postdischarge, median (IQR)	0 (2)	0 (1)	–0.03 (−0.46, 0.41) $P = .558$	-
SPPB				
From admission to discharge, mean (SD)	0.30 (2.17)	0.38 (1.75)‡	0.09 (−0.40, 0.57) $P = .732$	–0.06 (−0.53, 0.41) $P = .796$

Significant P values are in bold.
SPPB was not measured at baseline or at 3 months postdischarge. Within group differences in ADL function and performance in the SPPB were computed using Student paired t tests. Differences in FAC were computed using nonparametric tests (Mann Whitney U test and signed-rank test for unpaired and paired data, respectively), and could not be adjusted due to their nonparametric nature.
*Adjusted for baseline or admission values of the respective outcome measure.
†Significant within-group differences ($P < .001$).
‡Significant within-group differences ($P < .05$).

Table 4
Effects of Hospitalization on Study Endpoints

	Control Group (n = 25)		Exercise Group (n = 143)		Binary Logistic Regression/Negative Binomial Regression*	
	N with Actual Data for Analyses for Each Endpoint	Cases (%)	N with Actual Data for Analyses for Each Endpoint	Cases (%)	Crude (95% CI)	Adjusted (95% CI)†
At discharge						
HAD with reference to baseline‡	125	58	143	45	OR 0.59 (0.37, 0.96) $P = \mathbf{.035}$	OR 0.36 (0.17, 0.76) $P = \mathbf{.007}$
HAD with reference to admission	125	21	143	10	OR 0.41 (0.21, 0.83) $P = \mathbf{.013}$	OR 0.29 (0.10, 0.89) $P = \mathbf{.030}$
Dependent ambulation§	125	50	143	61	OR 1.53 (0.94, 2.48) $P = .087$	OR 0.62 (0.25, 1.54) $P = .302$
3-mo postdischarge						
HAD with reference to baseline	100	59	124	48	OR 0.65 (0.38, 1.11) $P = .114$	OR 0.44 (0.19, 1.03) $P = .058$
HAD with reference to admission	100	28	124	17	OR 0.52 (0.27, 0.99) $P = \mathbf{.048}$	OR 0.59 (0.21, 1.61) $P = .301$
Dependent ambulation	94	45	123	58	OR 1.69 (0.98, 2.90) $P = .057$	OR 0.77 (0.34, 1.76) $P = .541$
Rehospitalization	125	22	143	24	OR 1.12 (0.64, 1.98) $P = .689$	OR 1.48 (0.57, 3.84) $P = .423$
Number of falls‖	106	–	125	–	IRR: 0.98 (0.87, 1.08) $P = .678$	IRR: 0.98 (0.86, 1.14) $P = .678$
Mortality	125	10	143	4	OR 0.41 (0.15, 1.13) $P = .086$	OR 0.09 (0.01, 1.32) $P = .078$

CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio.
Significant ($P < .05$) OR values are in bold.
*The control group was used as reference for regression analyses; except for number of falls (analyzed with negative binomial regression), binary logistic regression was used for the remainder of endpoints.
†Adjusted for sex, age, body mass index, living or not at home, Charlson index, polypharmacy (≥7), comorbidities, cause of hospitalization (admission diagnosis), and physical function at admission (including Katz score, independent ambulation or not, and SPPB score). In the case of HAD from baseline, analyses were adjusted to physical function at the same time point.
‡HAD refers to the loss of ability to perform 1 or more basic ADLs independently at discharge.
§Dependent ambulation was considered in the event of a FAC <4.[19]
‖The number of falls was 0.19 ± 0.75 (median 0, range 0–6) and 0.17 ± 0.96 (median 0, range 0–10) for the control and intervention group, respectively.

has major negative consequences for patients and caregivers,[1] our results support the routine implementation of these exercises during the acute hospitalization of older patients.

Results of different systematic reviews indicate that inpatient exercise programs are safe and overall effective in hospitalized older patients.[12–14] However, not all types of exercise interventions are easily feasible in this population owing to a frequently limited mobility capacity. Walking during hospital stay has proven to maintain prehospitalization mobility, but conflicting results have been reported regarding its benefits on ADL function.[26,27] By contrast, the combination of walking with lower limb strengthening exercises can provide greater benefits on functional ability.[28,29] Indeed, walking combined with stretching/strengthening exercises (eg, leg lifts/swings, toe/heel raises) is associated with a better ADL function at 1-month postdischarge.[28] A recent study reported that a combination of walking, balance, and resistance exercises during a median of 5 days provided significant benefits in the functional ability and cognitive function of older patients during acute hospitalization.[29–31] But, the aforementioned intervention was more complex than the present protocol and required specific weight-training equipment,[29] which might hinder routine implementation in some ACE units.

Although sedentary behaviors (such as those commonly observed in hospitalized patients)[8] are associated with an increased incidence of frailty in older adults, the inclusion of a low amount of physical activity moderates (or even completely offsets if performed for >27 minutes) this relationship,[32] which reinforces the need of increasing physical activity levels regardless of the specific exercise performed. In further support of the effectiveness of simple exercises against sedentary behaviors and the consequent functional decline, Harvey et al[33] recently reported that encouraging frequent but small bouts of exercise (ie, rising from a chair) might suffice to reduce functional decline in frail sheltered housing residents. It is reasonable to hypothesize that, as in healthy older adults, a dose-response relationship likely exists between training intensity and exercise benefits.[34] However, our results suggest that walking and standing up from a chair (gradually increasing exercise loads by increasing the total number of repetitions and providing external help during the movement, if needed) might induce clinically meaningful benefits in the case of frail older patients such as those studied here. That said, this type of intervention requires close supervision and, thus, an additional time involvement of the hospital staff with respect to their daily duties or reliance on external staff, as described here (ie, fitness specialists).

Several potential limitations should be considered. The losses during the follow-up (up to ~20% of participants for some endpoints such as FAC) should be borne in mind as a limitation. Also, our study is a single-center study performed in a very old and frail population (ie, the proportion of participants who were fully independent in all the 6 ADLs at baseline was only 35%), which could limit the generalizability of our findings to younger or more functional patients. The small proportion (~25%) of the total number of hospitalized patients in our ACE unit who participated in our study possibly (partly because of the strict inclusion criteria) lends further support to the idea that the present results might not be necessarily applicable to acutely hospitalized old patients in general. On the other hand, no intervention effects were noted on relevant clinical measures at follow-up, including falls or rehospitalization. Finally, groups differed in functional and mental status at baseline/admission as well as in fall history, which might have potentially biased the study outcomes. Owing to their greater functional independence at baseline, patients in the control group might indeed have tended to more rapidly recover their "normal" physical status during hospitalization even in the absence of an exercise intervention. In this respect, however, the benefits of our intervention on incident HAD remained significant even after adjusting for clinical and functional variables at baseline or admission.

Although the intervention was effective to reduce HAD risk and did not require investment in weight-training equipment, the additional time commitment needed from the hospital staff to supervise the exercise sessions (or, alternatively, the need to rely on external staff such as fitness specialists, as we did here) are issues that should be addressed in future research, for instance, in studies aiming to assess the cost effectiveness of the present type of intervention.

Conclusions and Implications

A simple inpatient exercise program solely consisting of walking and rising from a chair (median duration of the intervention only 3 days, ~20 minutes/day) decreases the incidence of HAD in acutely hospitalized, very old patients and tends to enhance their ADL function. Further research is needed to analyze the cost-effectiveness of this type of intervention (in terms of staff resources) and its generalizability. However, given the clinical relevance of HAD, our results support the routine implementation of these exercises during the acute hospitalization of older patients.

Acknowledgments

We thank the geriatrics ward team for their valuable help and contribution to our results, with a special mention to the following professionals: Alison Martínez, Jaqueline Ferrero, Mar Alonso, Laura Arribas, Laura Osuna, Reyes Vaquerizo, Cristina Cebollero, Yolanda Navarro, Soledad Rubio, Ana Ruiz, Saray Martínez, Raquel Moreno, María Angeles Flores, Lidia del Campo, Azucena Ríos, Antonio Piñeiro, Manuela Gámez, Piedad Trujillo, Mayte Mesa, Raquel Gutiérrez, Ana Mª García, Mª Jesús Ruiz, Susana Palacios, Marta Orea, Ana Belén Huguet, Laura Jaro, Susana Robledo, José Lázaro.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2019.11.027.

References

1. Covinsky KE, Pierluissi E, Johnston CB. Hospitalization-associated disability "she was probably able to ambulate, but I'm not sure". JAMA 2011;306:1782–1793.
2. Gill TM, Allore HG, Holford TR, Guo Z. Hospitalization, restricted activity, and the development of disability among older persons. JAMA 2004;292:2115–2124.
3. Gill TM, Allore HG, Gahbauer E, Murphy T. Change in disability after hospitalization or restricted activity in older persons. JAMA 2010;304:1919–1928.
4. Covinsky KE, Palmer RM, Fortinsky RH, et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: Increased vulnerability with age. J Am Geriatr Soc 2003;51:451–458.
5. Boyd C, Landefeld C, Counsell S, et al. Recovery in activities of daily living among older adults following hospitalization for acute medical Illness. J Am Geriatr Soc 2008;56:2171–2179.
6. Inouye SK, Peduzzi PN, Robison JT, et al. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 1998;279:1187–1198.
7. Fortinsky RH, Covinsky KE, Palmer RM, Landefeld CS. Effects of functional status changes before and during hospitalization on nursing home admission of older adults. J Gerontol Ser A Biol Sci Med Sci 1999;54:521–526.
8. Brown CJ, Redden DT, Flood KL, Allman RM. The underrecognized epidemic of low mobility during hospitalization of older adults. J Am Geriatr Soc 2009;57:1660–1665.
9. Callen BL, Mahoney JE, Grieves CB, et al. Frequency of hallway ambulation by hospitalized older adults on medical units of an academic hospital. Geriatr Nurs 2004;25:212–217.
10. Valenzuela PL, Morales JS, Pareja-Galeano H, et al. Physical strategies to prevent disuse-induced functional decline in the elderly. Ageing Res Rev 2018;47:80–88.
11. Valenzuela P, Castillo-García A, Morales J, et al. Physical exercise in the oldest old. Compr Physiol 2019;9:1281–1304.
12. Martínez-Velilla N, Cadore EL, Casas-Herrero, et al. Physical activity and early rehabilitation in hospitalized elderly medical patients: Systematic review of randomized clinical trials. J Nutr Heal Aging 2016;20:738–751.

13. Bachmann S, Finger C, Huss A, et al. Inpatient rehabilitation specifically designed for geriatric patients: Systematic review and meta-analysis of randomised controlled trials. BMJ 2010;340:1230.
14. Kosse NM, Dutmer AL, Dasenbrock L, et al. Effectiveness and feasibility of early physical rehabilitation programs for geriatric hospitalized patients: A systematic review. BMC Geriatr 2013;13:1.
15. Fleck SJ, Bustamante-Ara N, Ortiz J, et al. Activity in GEriatric acute CARe (AGECAR): Rationale, design and methods. BMC Geriatr 2012;12:12–28.
16. Martínez de la Iglesia J, Herrero RD, Vilches MCO, et al. Adaptación y validación al castellano del cuestionario de Pfeiffer (SPMSQ) para detectar la existencia de deterioro cognitivo en personas mayores de 65 años. Med Clin (Barc) 2001; 117:129–134.
17. Vidán MT, Sánchez E, Alonso M, et al. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. J Am Geriatr Soc 2009;57:2029–2036.
18. Katz S, Ford A, Moskowitz R, et al. Studies of illnes in the aged. The index of ADL: A standardized measure of biological and pshychological function. JAMA 1963;185:914–918.
19. Holden MK, Gill KM, Magliozzi MR, et al. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther 1984;64: 35–40.
20. Rosanna Chau MW, Chan SP, Wong YW, Lau MYP. Reliability and validity of the modified functional ambulation classification in patients with hip fracture. Hong Kong Physiother J 2013;31:41–44.
21. Park CS, An SH. Reliability and validity of the modified functional ambulation category scale in patients with hemiparalysis. J Phys Ther Sci 2016;28: 2264–2267.
22. Tsang R, Chau R, Cheuk T, et al. The measurement properties of modified Rivermead mobility index and modified functional ambulation classification as outcome measures for Chinese stroke patients. Physiother Theory Pract 2014; 30:353–359.
23. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physcial performance battery assessing lower extremity function: Assocation with self-reported disability and prediction of mortality and nursing home admission. J Gerontol Med Sci 1994;49:M85–M94.
24. Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. Br Med J 2001;323:1123–1124.
25. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol Ser A Biol Sci Med Sci 2001;56:M146–M157.
26. Brown CJ, Foley KT, Lowman JD, et al. Comparison of posthospitalization function and community mobility in hospital mobility program and usual care patients a randomized clinical trial. JAMA Intern Med 2016;176:921–927.
27. Padula CA, Hughes C, Baumhover L. Impact of a nurse-driven mobility protocol on functional decline in hospitalized older adults. J Nurs Care Qual 2009;24: 325–331.
28. Siebens H, Aronow H, Edwards D, Ghasemi Z. A randomized controlled trial of exercise to improve outcomes of acute hospitalization in older adults. J Am Geriatr Soc 2000;48:1545–1546.
29. Martínez-Velilla N, Casas-Herrero N, Zambon-Ferraresi F, et al. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: A randomized clinical trial. JAMA Intern Med 2019;179: 28–36.
30. Saez de Asteasu ML, Martinez-Velilla N, Zambom-Ferraresi F, et al. Physical exercise improves function in acutely hospitalized older patients: Secondary analysis of a randomized clinical trial. J Am Med Dir Assoc 2019;20: 866–873.
31. Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, et al. Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: Secondary analysis of a randomized trial. PLOS Med 2019;16:e1002852.
32. Mañas A, Pozo-Cruz B, Rodríguez-Gómez I, et al. Can physical activity offset the detrimental consequences of sedentary time on frailty? A moderation analysis in 749 older adults measured with accelerometers. J Am Med Dir Assoc 2019; 20:634–638.e1.
33. Harvey JA, Chastin SFM, Skelton DA. Breaking sedentary behaviour has the potential to increase/maintain function in frail older adults. J Frailty Sarcopenia Falls 2018;03:26–34.
34. Borde R, Hortobágyi T, Granacher U. Dose–response relationships of resistance training in healthy old adults: A systematic review and meta-analysis. Sport Med 2015;45:1693–1720.

Supplementary Table 1
Effects of the Exercise Intervention on ADL Function: Subanalyses for Each of the 6 Specific ADLs Assessed With the Katz Index of Independence in ADLs

ADL	From Baseline to Discharge			From Admission to Discharge			From Baseline to 3 Mo			From Admission to 3 Mo		
	Control (n = 125), n (%)	Intervention (n = 143), n (%)	*P* value	Control (n = 125), n (%)	Intervention (n = 143), n (%)	*P* value	Control (n = 100), n (%)	Intervention (n = 124), n (%)	*P* value	Control (n = 100), n (%)	Intervention (n = 124), n (%)	*P* value
Bathing	31 (25)	30 (21)	.457	6 (5)	3 (3)	.312	27 (27)	24 (19)	.175	7 (7)	3 (2)	.115
Dressing	40 (32)	38 (27)	.329	11 (9)	5 (3)	.068	24 (24)	25 (20)	.490	9 (9)	4 (3)	.066
Toileting	35 (28)	45 (31)	.536	10 (8)	8 (6)	.433	28 (28)	27 (22)	.282	10 (10)	5 (4)	.076
Transferring	33 (28)	41 (29)	.678	10 (8)	7 (5)	.298	23 (23)	24 (19)	.505	11 (11)	6 (5)	.083
Continence	26 (21)	21 (15)	.189	16 (13)	5 (4)	**.005**	27 (27)	28 (23)	.445	22 (22)	14 (11)	**.030**
Feeding	12 (10)	13 (9)	.886	7 (6)	4 (3)	.249	16 (16)	20 (16)	.979	13 (13)	13 (10)	.559

Data represent the number (%) of participants in each group who lost the capacity to perform a specific activity independently. Differences between groups were computed using χ^2 tests (or Fisher exact test when more than 20% of cells had expected frequencies <5). Significant *P* values are in bold.

Supplementary Table 2
Effects of the Exercise Intervention on the SPPB: Subanalyses for Each of the 3 Tests of the SPPB

Individual Test	Control			Intervention			Unadjusted Difference Between Groups Mean (95% CI)	Adjusted Difference† Between Groups Mean (95% CI)
	Admission Mean (SD)	Discharge Mean (SD)	Change* Mean (SD)	Admission Mean (SD)	Discharge Mean (SD)	Change* Mean (SD)		
Balance	1.49 (1.29)	1.60 (1.34)	0.11 (1.21)	1.29 (1.26)	1.49 (1.29)	0.20 (1.14)‡	0.09 (−0.21, 0.38) *P* = .554	0.01 (−0.26, 0.28) *P* = .937
Gait ability	1.63 (1.28)	1.68 (1.21)	0.04 (1.00)	1.44 (1.03)	1.52 (0.99)	0.08 (0.84)	0.04 (−0.18, 0.25) *P* = .734	–0.03 (−0.22, 0.17)
Leg strength	0.75 (1.09)	0.89 (1.11)	0.14 (0.87)	0.46 (0.80)	0.56 (0.91)	0.10 (0.75)	–0.04 (−0.25, 0.16) *P* = .682	–0.13 (−0.32, 0.07) *P* = .194

Each test (balance, gait ability, and leg strength) is scored from 0 to 4, with a 0 to 12 sum-score for all 3 tests combined yielding the total SPPB score.
*Computed using paired Student *t*-tests.
†Adjusted for the performance attained in the respective test at admission.
‡Significant compared to admission (*P* = .043).

Individual responsiveness to physical exercise in acutely hospitalized older adults

With the aim of analyzing potential factors modulating individual responsiveness to inhospital exercise programs in older adults we performed a secondary analysis of the abovementioned clinical trial. This study was published in the *Journal of Clinical Medicine* (impact factor: 5,688, position 15/160, category: General medicine).[56] Our findings show that although exercise is overall effective for preventing HAD in older adults, a small proportion of patients present with this condition despite participating in the exercise program (known as 'adverse responders'), resulting in an impaired functional ability, physical performance and a greater risk of falls in the middle-term. Factors such as a longer hospital stay and a better functional and health status at baseline increased the odds of being adverse responder. A graphical abstract of this study is shown in Figure 5.

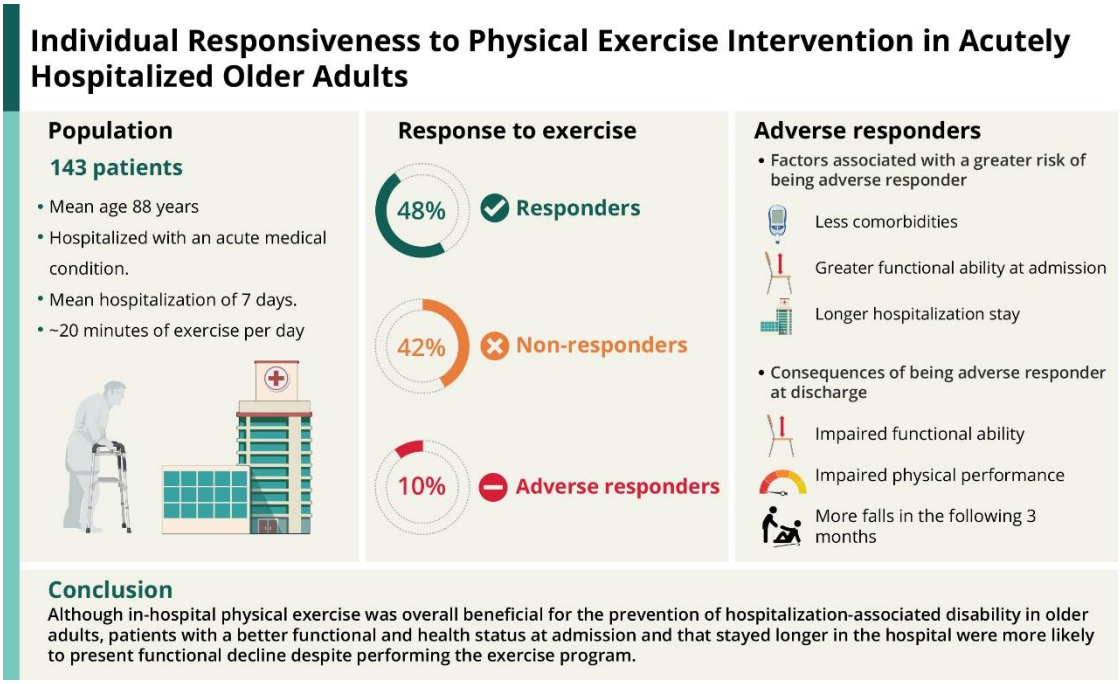


Figure 5. Rate of responsiveness to inhospital exercise in older adults, and factors associated with exercise responsiveness.

Journal of
Clinical Medicine

MDPI

Article

Individual Responsiveness to Physical Exercise Intervention in Acutely Hospitalized Older Adults

Pedro L. Valenzuela [1], Javier Ortiz-Alonso [2,3,4], Natalia Bustamante-Ara [5], María T. Vidán [2,3,4,6], Gabriel Rodríguez-Romo [4,7], Jennifer Mayordomo-Cava [3,4], Marianna Javier-González [2], Mercedes Hidalgo-Gamarra [2], Myriel López-Tatis [2], Maria Isabel Valadés-Malagón [2], Alejandro Santos-Lozano [8,9], José Antonio Serra-Rexach [2,3,4,6] and Alejandro Lucia [4,9,10,*]

1 Department of Systems Biology, University of Alcalá, 28801 Madrid, Spain; pedrol.valenzuela@edu.uah.es
2 Geriatrics Department, Hospital General Universitario Gregorio Marañón, 28007 Madrid, Spain; javier.ortiz@salud.madrid.org (J.O.-A.); maite.vidan@salud.madrid.org (M.T.V.); mariannajavier@gmail.com (M.J.-G.); mhidalgo7@hotmail.com (M.H.-G.); myriellopez@gmail.com (M.L.-T.); maribelvaladesmalagon@gmail.com (M.I.V.-M.); joseantonio.serra@salud.madrid.org (J.A.S.-R.)
3 Instituto de Investigación Sanitaria Gregorio Marañón, 28007 Madrid, Spain; jennifer.mayordomo@gmail.com
4 Biomedical Research Networking Centre on Frailty and Healthy Ageing, CIBERFES, 28029 Madrid, Spain; gabriel.rodriguez@upm.es
5 Facultad de Educación, Universidad Autónoma de Chile, 425 Talca, Chile; natalia_eba@yahoo.es
6 School of Medicine, Universidad Complutense, 28040 Madrid, Spain
7 Sports Department, Instituto Nacional de Educación Física, Universidad Politécnica de Madrid, 20040 Madrid, Spain
8 i+HeALTH, European University Miguel de Cervantes, 47012 Valladolid, Spain; asantos@uemc.es
9 Research Institute Hospital 12 de Octubre ('imas12'), 28041 Madrid, Spain
10 Faculty of Sport Sciences, Universidad Europea de Madrid, 28670 Madrid, Spain
* Correspondence: alejandro.lucia@universidadeuropea.es; Tel.: +34-916-647-800 (ext. 3010)

Received: 6 February 2020; Accepted: 6 March 2020; Published: 14 March 2020

Abstract: We analyzed inter-individual variability in response to exercise among acutely hospitalized oldest-old adults. In this ancillary analysis of a randomized controlled trial, 268 patients (mean age 88 years) were assigned to a control (n = 125, usual care) or intervention group (n = 143, supervised exercise, i.e., walking and rising from a chair [1–3 sessions/day]). Intervention group patients were categorized as responders, non-responders, or adverse responders (improved, no change, or impaired function in activities of daily living [ADL, Katz index] from hospital admission to discharge, respectively). We analyzed the association between responsiveness to exercise and variables assessed at baseline (2 weeks pre-admission), admission, during hospitalization, at discharge, and during a subsequent 3-month follow-up. An impaired ADL function and worse nutritional status at admission were associated to a greater responsiveness, whereas a better ADL function at admission, longer hospitalization and lower comorbidity index were associated with a poorer response ($p < 0.05$). Adverse responders had worse outcomes at discharge and during the follow-up (e.g., impaired physical performance and greater fall number) ($p < 0.05$). Although exercise intervention helps to prevent ADL function decline in hospitalized oldest-old people, a number of them—particularly those with a better functional/health status at admission and longer hospitalization—are at higher risk of being adverse responders, which can have negative short/middle-term consequences.

Keywords: hospital-associated disability; elders; functional ability; activities of daily living; training

1. Introduction

Hospitalization can have important negative consequences in older adults, notably an impaired capacity to perform activities of daily living (ADLs) independently. One of three hospitalized older adults suffers from hospital-associated disability (HAD), defined as the loss of the ability to perform one or more basic ADLs independently upon discharge compared to admission [1]. In turn, HAD is associated with several negative outcomes in the middle-long term, including a higher risk of nursing home admission [2], hospital readmission [3] and mortality [4]. Further, only ~30% of patients with this condition recover their pre-admission functional levels after one year [5].

The development of strategies aiming at preventing HAD should therefore be a priority [1,6]. In this context, although a number of factors can increase the risk of HAD [7–9], lack of physical activity during hospitalization seems particularly important. A recent study reported a mean daily non-sedentary time—that is, excluding sitting or lying in bed—of only one hour in hospitalized older adults, which in turn was associated with a greater HAD risk [10]. Strong evidence supports the beneficial role of in-hospital exercise programs to attenuate functional decline in older patients [11–13].

The study of the individual variability in response to exercise training is an emerging topic, especially in the context of "personalized medicine". Indeed, a considerable inter-individual variability is typically observed in the response to a given exercise intervention. Thus, some individuals show no benefits—or even negative adaptations—(i.e., "non-responders" or "adverse responders", respectively) after training programs that result overall beneficial in statistical terms [14]. However, scarce data are available in old adults, particularly in the "oldest old" people (i.e., ≥85 years) compared to younger individuals. In this regard, in a recent randomized controlled trial (RCT) from our group, a simple exercise intervention was found to be safe and to significantly reduce the prevalence of HAD in acutely hospitalized oldest old people (aged 88 years on average) compared to usual care [15]. Yet, 45% and 10% of the patients in the exercise group were discharged with an impaired ADL function compared to baseline and admission, respectively [15].

Whether the individual responses to exercise interventions in very old hospitalized people depend on some specific patients' characteristics (e.g., age, diagnosis at admission) remains unknown. This is an important question because, given the negative consequences of HAD [6], identifying potential factors predicting lack of response—and especially an adverse one—might allow us to target 'high-risk' patients. Moreover, previous research in hospitalized older adults has shown that a poor response to exercise is associated to negative outcomes (notably, increased mortality) after hospitalization [16]. Thus, the analysis of inter-individual variability might help to identify those people who might benefit from more targeted or personalized exercise interventions in order to prevent the negative functional consequences of hospitalization.

It was therefore the purpose of this ancillary analysis of our recent RCT [15] to analyze inter-individual variability in response to a physical exercise intervention in acutely hospitalized older adults as well as the potential predictors of the different types of responses. We also analyzed the short and middle term functional and health consequences of the different types of responses. Attending to the results reported by our group in other clinical populations [17,18], we hypothesized that a poorer response would be observed in those individuals with a greatest physical fitness before hospitalization. Moreover, following recent data from Saez de Asteasu et al. [16], we hypothesized that adverse responders would present with poorer outcomes (e.g., impaired physical performance) at both discharge and during post-hospitalization follow-up.

2. Material and Methods

2.1. Study Design

The details of our recent RCT are shown elsewhere [15]. Briefly, acutely hospitalized older adults were randomized to a control (usual care) or intervention group (usual care + supervised exercise). For the present study, only patients in the intervention group were assessed, and categorized as either

responders (positive change), non-responders (no change), or adverse responders (negative change). We analysed the association between responsiveness to the exercise intervention, and different variables assessed at baseline (i.e., two weeks before admission) and admission, and during hospitalization.

The study was approved by the local Ethics Committee (Hospital Universitario Gregorio Marañón, Madrid, Spain; reference # 107/11; approved on 3 May 2011), and written informed consent was obtained from patients. When it was not possible to obtain the informed consent directly from a patient due to medical reasons (e.g., impaired cognitive function), proxy consent was obtained from their relatives. All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2. Participants

Patients (>75 years) admitted to our Acute Care for Elders unit were considered eligible to participate, excluding those who met the following criteria: non-ambulatory or dependent in all basic ADLs at baseline (i.e., two weeks before admission, as assessed by retrospective interview); having unstable cardiovascular disease (or any other major medical condition contraindicating exercise), terminal illness, or severe dementia (i.e., ≥8 errors in the Spanish version of the short portable mental status questionnaire [SPMSQ], also known as Pfeiffer's test) [19]; expected length of hospitalisation <3 days; being transferred from another hospital unit; or having a scheduled admission (which was usually associated with a length of hospitalisation <3 days) [15]. All participants received the standard care in our unit (including the standard diet adapted to their disease [notably, diabetes and renal insufficiency] and specific necessities).

2.3. Intervention

Besides receiving standard care in our unit, patients in the intervention group participated in a supervised in-hospital exercise programme. Exercise sessions (Monday to Friday, from one to three sessions per day [depending on the patient's physical capacity] conducted on both mornings and afternoons) consisted of rising from a seated to an upright position (using armrests/assistance if necessary) and walking exercises. For the former, exercise loads increased individually and progressively from one to three sets of up to 10 repetitions, with a two-minute rest between sets. When patients could complete the prescribed training session (e.g., one set of 10 repetitions) in two consecutive days, a new set was added, up to a maximum of three sets of 10 repetitions per session. Total walking time progressed from three to 10 min (with resting periods if needed, depending on the patient's condition) along the corridor of the ward with assistance if necessary. Standing and walking exercises were separated by a rest period of up to five minutes. All exercise sessions were supervised by fitness specialists.

2.4. Responsiveness Analysis

ADL function was assessed with the Katz index, which measures patients' ability to independently perform six basic ADLs (eating, transferring from bed to chair, walking, using the toilet, bathing, and dressing), each of which is scored with zero or one depending on whether the participant is able to perform the activity with or without help, respectively [20]. Nurses who were not involved in supervising the intervention were in charge of the assessment of ADL function. However, assessors and care providers were not blinded to the assigned intervention.

Responsiveness was defined attending to clinically meaningful changes, which in the case of ADL function was considered as gaining or losing the ability to independently perform one or more ADLs from hospital admission to discharge. Thus, participants were considered responders (gaining one or more ADLs from hospital admission to discharge), non-responders (no change in any ADL from hospital admission to discharge), or adverse responders (losing one or more ADLs from hospital admission to discharge).

2.5. Outcomes

We analysed the association between exercise responsiveness and different variables assessed at baseline (i.e., two weeks before admission, as assessed retrospectively through a standardized interview with patients or their caregivers), at admission, and during hospitalization. These variables included demographic (age, sex) and clinical characteristics (diagnosis at admission, presence of other geriatric syndromes [dementia, depression, falls, chronic pain, malnutrition, urinary incontinence, frailty phenotype, incident delirium], comorbidities [assessed by means of the Charlson comorbidity index] [21], polypharmacy [taking ≥ 7 drugs] or frailty [having ≥3 of the 5 Fried's criteria]) [22]. The association between responsiveness and ADL function, ambulatory capacity (assessed by means of the modified Functional Ambulatory Categories [FAC]) [23] and physical performance (measured with the Short Physical Performance Battery [SPPB]) [24] at baseline or admission was also assessed; as well as the association between responsiveness, and the length of hospital stay and exercise loads (frequency [number of training days] and volume [i.e., total number of sit-ups and walking time]).

We also assessed the association of responsiveness to the intervention with ADL function, FAC and SPPB at discharge and after a 3-month follow-up–except for SPPB, which could not be assessed at follow-up; as well as with mortality and number of falls during the 3-month follow-up (registered by telephone interview).

2.6. Statistical Analysis

The exact details for the determination of the optimal sample size are available elsewhere [15]. Based on previous (unpublished) data obtained in our ACE unit, we determined that 33% of the patients improved their ADL from admission to discharge—and could be therefore considered responders. Based on previous reports [16–18], we aimed to achieve a rate of responsiveness of ~50%, and we therefore estimated a minimum sample of 138 participants for the intervention group (power = 95%, $\alpha = 0.05$).

Data are presented as mean ± standard deviation (SD) unless otherwise stated. Chi-squared tests and one-way analyses of variance (ANOVA) were performed to assess differences between responders, non-responders and adverse responders to the intervention for dichotomous and continuous outcomes, respectively. The likelihood of responsiveness to the intervention attending to different variables assessed at baseline, admission or during hospitalization was determined using univariate logistic regression analyses. Multivariate logistic regression model was fitted for those variables showing a p-value ≤ 0.157 in the univariate analyses [25]. We also analyzed the association between responsiveness and different outcomes at discharge and during the subsequent 3-month follow-up using binary logistic regression (for dichotomous outcomes) or linear regression (for continuous outcomes). All statistical analyses were conducted using a statistical software package (SPSS 23.0, IBM, NY) with $\alpha = 0.05$.

3. Results

The characteristics of the participants in the intervention group are summarized in Table 1. They had a mean age of 88 ± 5 years (range 75–102). The median length of hospitalisation was 7 days (interquartile range [IQR] 4), with no differences between responder groups, albeit with a non-significant trend ($p = 0.085$) towards a longer hospital stay in adverse responders. No between-group differences were found for demographic or clinical variables at admission (all $p > 0.05$, Table 1). However, responders had a greater loss of ADL function from baseline to admission and a lower ADL function at admission than both non-responders ($p = 0.018$ and $p = 0.010$, respectively) and adverse responders ($p = 0.088$ and 0.005) (Table 1).

Table 1. Main characteristics of responders, non-responders or adverse responders to the exercise intervention attending to the change (i.e., improvement, no change or decrease, respectively) in functional ability (i.e., ability to perform activities of daily living [ADLs] independently) during hospitalization.

Variable	Responder (N = 69)	Non-Responder (N = 60)	Adverse Responder (N = 14)
Age (years; mean [SD])	88 (5)	88 (5)	88 (5)
Sex (female) (%)	60.9%	58.3%	64.3%
Body mass index (kg·m^{-2}; mean [SD])	26.3 (5.4)	25.6 (4.6)	25.3 (5.9)
Charlson comorbidity index (mean [SD])	6.8 (1.7)	6.8 (1.6)	5.7 (1.1)
Polypharmacy (≥7) (%)	55.1	65.0	42.9
Geriatric syndromes at admission (%)			
Dementia	21.7	28.3	42.9
Depression	29.0	35.0	35.7
Falls	30.4	41.7	42.9
Chronic pain	31.9	35.0	50.0
Malnutrition	14.5	30.0	21.4
Urinary incontinence	46.4	51.7	50.0
Frailty phenotype	68.1	66.7	78.6
Incident delirium	18.8	21.7	14.3
Main admission diagnosis (n [%])			
Respiratory	24.6	33.3	28.6
Circulatory	7.2	5.0	7.1
Renal/urologic	11.6	13.3	7.1
Central nervous system	11.6	10	14.3
ADL function at baseline (mean [SD])	3.9 (1.8)	4.0 (1.9)	4.5 (1.5)
FAC score at baseline (mean [SD])	3.5 (0.9)	3.4 (0.9)	3.2 (1.1)
ADL function at admission (mean [SD])	1.7 (1.8)	2.7 (2.1) *	3.4 (1.3) **
FAC score at admission (mean [SD])	2.2 (1.3)	2.5 (1.4)	2.7 (1.4)
Loss of ADL from baseline to admission (mean [SD])	2.2 (2.0)	1.4 (1.7) *	1.1 (0.8)
SPPB score at admission (mean [SD])	3.1 (2.3)	3.5 (2.7)	2.5 (2.1)
Length of hospitalization (days; median [IQR])	6 (4.5)	6 (3)	8 (7.5)
Training days (median [IQR])	3 (2)	2 (2)	3 (3)
Daily walking volume (minutes; mean [SD])	15 (8)	16 (9)	13 (11)
Total walking volume (minutes; mean [SD])	47 (35)	41 (37)	46 (39)
Daily number of sit-ups (mean [SD])	29 (20)	27 (19)	23 (24)
Total number of sit-ups (mean [SD])	90 (77)	74 (71)	84 (71)

Abbreviations: FAC, functional ambulation category; IQR, interquartile range; SD, standard deviation; SPPB, short physical performance battery. Significant *p*-values are in bold. Significantly different from responders: * $p < 0.05$, ** $p < 0.01$.

Multivariate logistic regression analyses showed that ADL function at admission was negatively associated with the odds of being a responder, whereas malnutrition was positively associated (Figure 1 and Table S1). On the other hand, both ADL function at admission and the length of hospitalization were positively associated with the likelihood of being an adverse responder, whereas a negative association was found for dementia and Charlson comorbidity index.

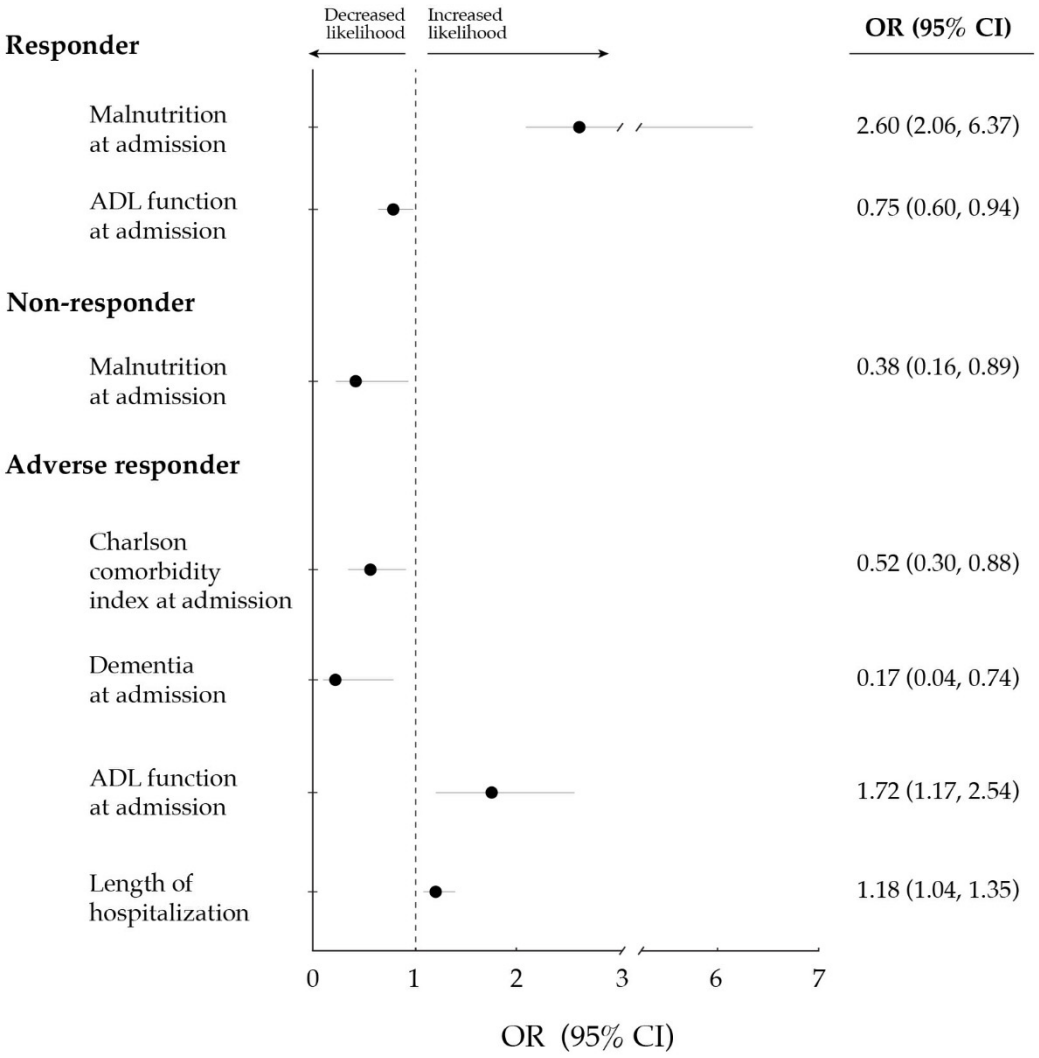


Figure 1. Significant ($p < 0.05$) associations between: (i) demographic and clinical variables at baseline (i.e., two weeks before hospitalization) or upon hospital admission; and (ii) the response of functional ability (i.e., ability to perform activities of daily living [ADLs] independently) to the exercise intervention (i.e., responder [improvement], non-responder [no change] or adverse responder [decrease]). Data are shown as odds ratio (OR) along with 95% confidence interval (CI), and were computed through multivariate logistic regression analyses (fitted for those variables showing a p-value ≤ 0.157 in univariate analyses).

Being a responder was positively associated with ADL function as well as with ambulatory capacity and physical performance at discharge, whereas the opposite was observed for adverse responders (Figure 2 and Table S2). Moreover, being an adverse responder was positively associated with the number of falls sustained during the 3-month follow-up after discharge, although no association was observed for other outcomes such as ADL function, ambulatory capacity, re-hospitalization or mortality during the follow-up.

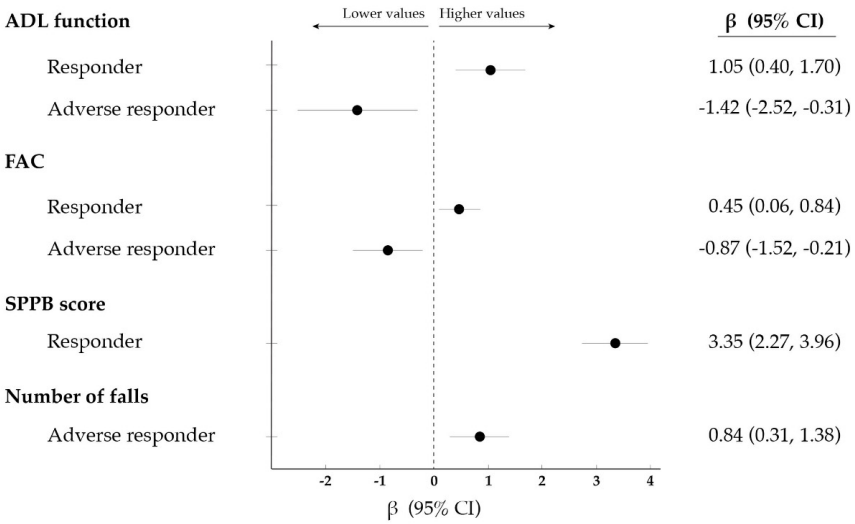


Figure 2. Significant ($p < 0.05$) association between: (i) the response of functional ability (i.e., ability to perform activities of daily living [ADL] independently) to the exercise intervention (i.e., responder, non-responder or adverse responder to exercise (i.e., responder [improvement], non-responder [no change] or adverse responder [decrease]); and (ii) different outcomes at discharge or during a 3-month follow-up. Data were analysed using linear regression and are expressed as β along with 95% confidence intervals (CI). No significant associations were found for non-responders. Abbreviations: FAC, functional ambulatory category; SPPB, short physical performance battery.

4. Discussion

The present study shows that, although a physical exercise intervention was safe and overall reduced the prevalence of HAD in acutely hospitalized older adults, a high proportion of patients showed no improvement (~40%) or even an impairment (~10%) in ADL function during hospitalization despite receiving the aforementioned intervention. A lack of response—or even a negative one—to exercise was particularly evident in those patients with longer in-hospital stays and a better health (i.e., less comorbidities) and functional status (i.e., greater ADL function) before hospitalization. Conversely, a better response was found in those patients who had a lower ADL function at hospital admission or had malnutrition. Identification of potential predictors of a poor, and especially adverse, response to the intervention is of clinical relevance. Indeed, an adverse response was associated to poorer outcomes at both discharge (impaired ADL function, ambulatory capacity and physical performance) and during the 3-month follow-up (i.e., greater number of falls).

Although our exercise program proved to be overall beneficial to ADL function, which is in line with previous research [11,12,26–28], 52% of the participants in the intervention group did not improve their ADL function during hospitalization or were even discharged with an impaired ADL function compared to hospital admission. Similar results have been recently reported for hospitalized oldest old adults (mean age 87 years) by Saez de Asteasu et al. [16]. These authors found that 15%, 49% and 38% of the participants in the exercise group obtained no benefits (or even a deterioration) in some functional outcomes (physical performance, gait velocity, and muscle strength) despite the intervention being safe and overall beneficial compared to usual care. Thus, our results provide additional evidence in support of the beneficial effects of physical exercise for oldest old people and particularly for those who are hospitalized—which include improvements not only in muscle mass/strength, but also in cardiorespiratory fitness, in inflammatory and hormonal status, or cognitive function [29]. However, taken together, previous [16] and present results support that there is a considerable individual variability in the response to an in-hospital intervention for very old patients.

The present study also shows that, except for those with dementia—who had a lower likelihood of being adverse responders—patients with a better functional/health status at admission seemed to

suffer from a greater functional decline during hospitalization despite participating in our exercise program. Conversely, their peers with a poorer functional status seemed to be those benefiting more from the program. In line with our findings, Jones et al. [30] recently observed that although an exercise intervention was overall not effective for the improvement of ADL function in hospitalized older adults, patients with a low baseline functional status benefited from the intervention. Previous research from our group has also reported greater benefits in those individuals with a poorer fitness level at baseline in other clinical populations including children with cancer [17] or haemodialysis patients [18].

The sedentary lifestyle that characterizes hospitalized older adults could contribute to the marked functional decline that they usually suffer, particularly during long hospital stays. Indeed, different studies have reported that hospitalised older adults spend most of the time in bed even when they are able to walk independently [31,32], with the levels of inactivity being related to the risk of HAD [10]. Increasing activity levels should therefore be a priority, especially in those patients with a better functional status at admission, with the latter theoretically allowing to maintain a more active lifestyle during the whole hospital stay. In the present study, we applied a simple exercise intervention solely consisting of walking and rising from a chair, which might not represent a stimulus high enough for the fittest patients. Thus, we could hypothesize that the response to the exercise intervention might have had a ceiling effect, with those patients with greater fitness levels needing more demanding interventions (i.e., longer and/or more intense programs) to obtain meaningful benefits. In this context, multi-component exercise interventions applying greater volumes or higher intensities (e.g., resistance training with fast or 'explosive' movements) might be more effective in these fitter patients, as previously reported for older adults who were overall fitter at baseline than our participants [29,33,34]. A number of studies have previously reported that implementation of higher training loads can enhance responsiveness in individuals who were classified a priori as non-responders [35,36]. Moreover, increasing exercise intensity has been reported to result in a greater release of muscle-derived factors (also known as "myokines", e.g., fibroblast growth factor, follistatin) that are known to induce positive cardiometabolic effects (e.g., enhanced glucose homeostasis and lipid utilization) and facilitate muscle anabolism [37]. In the same line, compared with moderate-intensity exercise, a higher exercise intensity provides larger benefits on other variables such as blood pressure, glucose control and aerobic fitness [38]. Thus, future research should determine the safety and effectiveness at the individual level of tailored in-hospital exercise interventions for oldest old people of higher intensity than the one applied here.

Another relevant finding was that adverse responders presented with impaired functional capacity (lower ADL function, ambulatory capacity and physical performance) at discharge and a greater incidence of falls during the 3-month follow-up. Of note, lower levels of both ADL function and physical performance at discharge have been associated with negative outcomes (long-term functional impairment, institutionalization, re-hospitalisation, death) after acute hospitalisation in old people [6,39,40]. Moreover, Saez de Asteasu et al. [16] recently reported that those participants who were adverse responders for physical performance (SPPB) tended to have a higher risk of mortality during a one-year follow-up after hospitalization. Taken together, present and previous results [16] overall support the negative consequences of HAD in hospitalized older adults, and highlight the need for maximizing exercise responsiveness in this patient population.

Some limitations must be acknowledged. We analyzed responsiveness for a single outcome such as ADL function because our exercise intervention provided no significant benefits in other functional measures such as SPPB or FAC [15]. Future research should confirm if other types of exercise interventions (e.g., involving multicomponent exercises) can provide benefits for these variables. Different procedures have been used in the literature for the determination of responsiveness that could not be applied in the context of our study. Responsiveness has been considered by other authors as an improvement greater than the technical standard error of measurement or greater than the between-day variability—or both—for the outcome measure/s in question, which should control for the random error of measurement [17,18,41]. However, responsiveness can also be determined attending

to whether the observed changes are clinically relevant [41]. In this regard, given the relevance of ADL function per se, in the present study we determined responsiveness based on clinically meaningful changes, that is, attending to the changes in the ability to independently perform ADLs. Our findings in fact confirm the clinical relevance of ADL function per se, as adverse-responders presented with poorer outcomes at both discharge and during the follow-up. On the other hand, it must be noted that participants, assessors, and care providers were not blinded to the intervention assigned to each participant, which can be considered as a limitation of our study. Finally, we did not assess some important variables such as nutritional intake (notably, of proteins), emotional status, or physical activity levels outside the exercise intervention—all of which can influence the functional response to hospitalization—and thus our analyses were not controlled for these potential confounders. Future research should assess the influence of these variables on the risk of a poor response to in-hospital exercise in the oldest old.

5. Conclusions

Although in-hospital physical exercise was safe and overall beneficial for the prevention of HAD in acutely hospitalized older adults, there was individual variability in the responses of ADL function to the intervention. Patients with a worse functional status at admission were likely to respond more positively to the exercise program. By contrast, those who stayed longer in the hospital and who had a better ADL function and less comorbidities at admission—except dementia—were more likely to suffer from HAD despite performing the exercise program. The latter group of patients should be potentially targeted, in terms of ensuring that exercise loads are sufficiently high and of promoting a lifestyle as active as possible during hospitalization.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/3/797/s1, Table S1: Association between demographic and clinical variables and the response to the exercise intervention. Table S2: Association between the response to the exercise intervention and different outcomes at discharge or during a 3-month follow-up.

Author Contributions: Conceptualization, P.L.V., J.O.-A., N.B.-A., M.T.V., G.R.-R., A.L. and J.A.S.-R.; methodology, J.M.-C., M.J.-G., M.H.-G., M.L.-T. and M.I.V.-M.; formal analysis, P.L.V. and A.S.-L.; writing—original draft preparation, P.L.V. and A.L.; writing—review and editing, all authors; project administration, J.O.-A., A.L. and J.A.S.-R.; funding acquisition, A.L. and J.A.S.-R. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Instituto de Salud Carlos III (Ministerio de Ciencia, Innovación y Universidades, Spain) (RD12/0043/0025, PI12/02852, PI15/00558 and PI18/00139); Biomedical Research Networking Center on Frailty and Healthy Aging (CIBERFES, Spain); and FEDER funds from the European Union. The work of Pedro L. Valenzuela is supported by a contract granted by the University of Alcalá (FPI2016).

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Loyd, C.; Markland, A.D.; Zhang, Y.; Fowler, M.; Harper, S.; Wright, N.C.; Carter, C.S.; Buford, T.W.; Smith, C.H.; Kennedy, R.; et al. Prevalence of hospital-associated disability in older adults: A meta-analysis. *J. Am. Med. Dir. Assoc.* **2019**, in press. [CrossRef] [PubMed]
2. Fortinsky, R.H.; Covinsky, K.E.; Palmer, R.M.; Landefeld, C.S. Effects of functional status changes before and during hospitalization on nursing home admission of older adults. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **1999**, *54*, 521–526. [CrossRef] [PubMed]
3. Tonkikh, O.; Shadmi, E.; Flaks-Manov, N.; Hoshen, M.; Balicer, R.D.; Zisberg, A. Functional status before and during acute hospitalization and readmission risk identification. *J. Hosp. Med.* **2016**, *11*, 636–641. [CrossRef] [PubMed]
4. Inouye, S.K.; Peduzzi, P.N.; Robison, J.T.; Hughes, J.S.; Horwitz, R.I.; Concato, J. Importance of functional measures in predicting mortality among older hospitalized patients. *JAMA* **1998**, *279*, 1187–1198. [CrossRef]

5. Boyd, C.; Landefeld, C.; Counsell, S.; Palmer, R.; Fortinsky, R.; Kresevic, D.; Burant, C.; Covinsky, K. Recovery in activities of daily living among older adults following hospitalization for acute medical illness. *J. Am. Geriatr. Soc.* **2008**, *56*, 2171–2179. [CrossRef]
6. Covinsky, K.E.; Pierluissi, E.; Johnstone, C.B. Hospitalization-associated disability "She was probably able to ambulate, but i'm not sure". *JAMA* **2011**, *306*, 1782–1793. [CrossRef]
7. Covinsky, K.E.; Palmer, R.M.; Fortinsky, R.H.; Counsell, S.R.; Stewart, A.L.; Kresevic, D. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: Increased vulnerability with age. *J. Am. Geriatr. Soc.* **2003**, *51*, 451–458. [CrossRef]
8. Buurman, B.M.; Hoogerduijn, J.G.; van Gemert, E.A.; de Haan, R.J.; Schuurmans, M.J.; de Rooij, S.E. Clinical characteristics and outcomes of hospitalized older patients with distinct risk profiles for functional decline: A prospective cohort study. *PLoS ONE* **2012**, *7*, e29621. [CrossRef]
9. Van Seben, R.; Reichardt, L.A.; Aarden, J.J.; van der Schaaf, M.; van der Esch, M.; Engelbert, R.H.H.; Twisk, J.W.R.; Bosch, J.A.; Buurman, B.M.; Kuper, I.; et al. The course of geriatric syndromes in acutely hospitalized older adults: The hospital-ADL study. *J. Am. Med. Dir. Assoc.* **2019**, *20*, 152–158.e2. [CrossRef]
10. Pavon, J.M.; Sloane, R.J.; Pieper, C.F.; Colón-Emeric, C.S.; Cohen, H.J.; Gallagher, D.; Hall, K.S.; Morey, M.C.; McCarty, M.; Hastings, S.N. Accelerometer-measured hospital physical activity and hospital-acquired disability in older adults. *J. Am. Geriatr. Soc.* **2019**, in press. [CrossRef]
11. Bachmann, S.; Finger, C.; Huss, A.; Egger, M.; Stuck, A.E.; Clough-Gorr, K.M. Inpatient rehabilitation specifically designed for geriatric patients: Systematic review and meta-analysis of randomised controlled trials. *BMJ* **2010**, *340*, c1718. [CrossRef] [PubMed]
12. Kosse, N.M.; Dutmer, A.L.; Dasenbrock, L.; Bauer, J.M.; Lamoth, C.J.C. Effectiveness and feasibility of early physical rehabilitation programs for geriatric hospitalized patients: A systematic review. *BMC Geriatr.* **2013**, *13*, 107. [CrossRef] [PubMed]
13. Heldmann, P.; Werner, C.; Belala, N.; Bauer, J.M.; Hauer, K. Early inpatient rehabilitation for acutely hospitalized older patients: A systematic review of outcome measures. *BMC Geriatr.* **2019**, *19*, 189. [CrossRef] [PubMed]
14. Mann, T.; Lamberts, R.; Lambert, M. High responders and low responders: Factors associated with individual variation in response to standardized training. *Sports Med.* **2014**, *44*, 1113–1124. [CrossRef] [PubMed]
15. Ortiz-alonso, J.; Bustamante-Ara, N.; Valenzuela, P.L.; Vidán, M.; Rodríguez-Romo, G.; Mayordomo-Cava, J.; Javier-González, M.; Hidalgo-gamarra, M.; López-Tatis, M.; Valades-Malagón, I.; et al. Effect of a simple exercise programme on hospitalisation-associated disability in older patients: A randomised controlled trial. *JAMDA* **2019**, in press.
16. Sáez de Asteasu, M.L.; Martínez-Velilla, N.; Zambom-Ferraresi, F.; Casas-Herrero, Á.; Cadore, E.L.; Ramirez-Velez, R.; Izquierdo, M. Inter-individual variability in response to exercise intervention or usual care in hospitalized older adults. *J. Cachexia Sarcopenia Muscle* **2019**, *10*, 1266–1275. [CrossRef]
17. Morales, J.S.; Padilla, J.R.; Valenzuela, P.L.; Santana-Sosa, E.; Rincón-Castanedo, C.; Santos-Lozano, A.; Herrera-Olivares, A.M.; Madero, L.; Juan, A.F.S.; Fiuza-Luces, C.; et al. Inhospital exercise training in children with cancer: Does it work for all? *Front. Pediatr.* **2018**, *6*, 404. [CrossRef]
18. Valenzuela, P.L.; de Alba, A.; Pedrero-Chamizo, R.; Morales, J.S.; Cobo, F.; Botella, A.; González-Gross, M.; Pérez, M.; Lucia, A.; Marín-López, M.T. Intradialytic exercise: One size doesn't fit all. *Front. Physiol.* **2018**, *9*, 844. [CrossRef]
19. Martínez de la Iglesia, J.; Herrero, R.D.; Vilches, M.C.O.; Taberné, C.A.; Colomer, C.A.; Luque, R.L. Adaptación y validación al castellano del cuestionario de Pfeiffer (SPMSQ) para detectar la existencia de deterioro cognitivo en personas mayores de 65 años. *Med. Clin.* **2001**, *117*, 129–134. [CrossRef]
20. Katz, S.; Ford, A.; Moskowitz, R.; Jackson, B.; Jaffe, M. Studies of illnes in the aged. The index of ADL: A standardized measure of biological and pshychological function. *JAMA* **1963**, *185*, 914–918. [CrossRef]
21. Charlson, M.; Szatrowski, T.P.; Peterson, J.; Gold, J. Validation of a combined comorbidity index. *J. Clin. Epidemiol.* **1994**, *47*, 1245–1251. [CrossRef]
22. Fried, L.P.; Tangen, C.M.; Walston, J.; Newman, A.B.; Hirsch, C.; Gottdiener, J.; Seeman, T.; Tracy, R.; Kop, W.J.; Burke, G.; et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2001**, *56*, M146–M157. [CrossRef] [PubMed]
23. Holden, M.K.; Gill, K.M.; Magliozzi, M.R.; Nathan, J.; Piehl-baker, L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. *Phys. Ther.* **1984**, *64*, 35–40. [CrossRef] [PubMed]

24. Guralnik, J.M.; Simonsick, E.M.; Ferrucci, L.; Glynn, R.J.; Berkman, L.F.; Blazer, D.G.; Scherr, P.A.; Wallace, R.B. A short physcial performance battery assessing lower extremity function: Assocation with self-reported disability and prediction of mortality and nursing home admission. *J. Gerontol. Med. Sci.* **1994**, *49*, M85–M94. [CrossRef]
25. Heinze, G.; Dunkler, D. Five myths about variable selection. *Transpl. Int.* **2017**, *30*, 6–10. [CrossRef]
26. Martínez-Velilla, N.; Cadore, E.L.; Casas-Herrero, A.; Idoate-Saralegui, F.; Izquierdo, M. Physical activity and early rehabilitation in hospitalized elderly medical patients: Systematic review of randomized clinical trials. *J. Nutr. Health Aging* **2016**, *20*, 738–751. [CrossRef]
27. Martínez-Velilla, N.; Casas-Herrero, N.; Zambon-Ferraresi, F.; López Sáez de Asteasu, M.; Lucia, A.; Galbete, A.; García-Baztán, A.; Alonso-Renedo, J.; González-Glaría, B.; Gonzalo-Lázaro, M.; et al. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: A randomized clinical trial. *JAMA Intern. Med.* **2019**, *179*, 28–36. [CrossRef]
28. Killey, B.; Watt, E. The effect of extra walking on the mobility, independence and exercise self-efficacy of elderly hospital in-patients: A pilot study. *Contemp. Nurse* **2006**, *22*, 120–133. [CrossRef]
29. Valenzuela, P.; Castillo-García, A.; Morales, J.; Izquierdo, M.; Serra-Rexach, J.; Santos-Lozano, A.; Lucia, A. Physical exercise in the oldest old. *Compr. Physiol.* **2019**, *9*, 1281–1304.
30. Jones, C.T.; Lowe, A.J.; MacGregor, L.; Brand, C.A.; Tweddle, N.; Russell, D.M. A randomised controlled trial of an exercise intervention to reduce functional decline and health service utilisation in the hospitalised elderly. *Australas. J. Ageing* **2006**, *25*, 126–133. [CrossRef]
31. Brown, C.J.; Redden, D.T.; Flood, K.L.; Allman, R.M. The underrecognized epidemic of low mobility during hospitalization of older adults. *J. Am. Geriatr. Soc.* **2009**, *57*, 1660–1665. [CrossRef] [PubMed]
32. Callen, B.L.; Mahoney, J.E.; Grieves, C.B.; Wells, T.J.; Enloe, M. Frequency of hallway ambulation by hospitalized older adults on medical units of an academic hospital. *Geriatr. Nurs.* **2004**, *25*, 212–217. [CrossRef] [PubMed]
33. Straight, C.R.; Lindheimer, J.B.; Brady, A.O.; Dishman, R.K.; Evans, E.M. Effects of resistance training on lower-extremity muscle power in middle-aged and older adults: A systematic review and meta-analysis of randomized controlled trials. *Sports Med.* **2016**, *46*, 353–364. [CrossRef] [PubMed]
34. Tschopp, M.; Sattelmayer, M.K.; Hilfiker, R. Is power training or conventional resistance training better for function in elderly persons? A meta-analysis. *Age Ageing* **2011**, *40*, 549–556. [CrossRef] [PubMed]
35. Montero, D.; Lundby, C. Refuting the myth of non-response to exercise training: 'Non-responders' do respond to higher dose of training. *J. Physiol.* **2017**, *595*, 3377–3387. [CrossRef] [PubMed]
36. Ross, R.; de Lannoy, L.; Stotz, P.J. Separate effects of intensity and amount of exercise on interindividual cardiorespiratory fitness response. *Mayo Clin. Proc.* **2015**, *90*, 1506–1514. [CrossRef] [PubMed]
37. He, Z.; Tian, Y.; Valenzuela, P.L.; Huang, C.; Zhao, J.; Hong, P.; He, Z.; Yin, S.; Lucia, A. Myokine/adipokine response to "aerobic" exercise: Is it just a matter of exercise load? *Front. Physiol.* **2019**, *10*, 691. [CrossRef]
38. Swain, D.P.; Franklin, B.A. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. *Am. J. Cardiol.* **2006**, *97*, 141–147. [CrossRef]
39. Volpato, S.; Cavalieri, M.; Sioulis, F.; Guerra, G.; Maraldi, C.; Zuliani, G.; Fellin, R.; Guralnik, J.M. Predictive value of the short physical performance battery following hospitalization in older patients. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2011**, *66 A*, 89–96. [CrossRef]
40. Corsonello, A.; Lattanzio, F.; Pedone, C.; Garasto, S.; Laino, I.; Bustacchini, S.; Pranno, L.; Mazzei, B.; Passarino, G.; Incalzi, R.A. Prognostic significance of the short physical performance battery in older patients discharged from acute care hospitals. *Rejuvenation Res.* **2012**, *15*, 41–48. [CrossRef]
41. Hecksteden, A.; Pitsch, W.; Rosenberger, F.; Meyer, T. Repeated testing for the assessment of individual response to exercise training. *J. Appl. Physiol.* **2018**, *124*, 1567–1579. [CrossRef] [PubMed]

Effects of exercise on the functional status of acutely hospitalized older adults

With the aim of compiling the evidence on the effectiveness of inhospital exercise programs for preventing functional decline in older adults admitted with an acute medical condition, we performed a systematic review and meta-analysis that was published in *Ageing Research Reviews* (impact factor 10.390, position 2/53, category: Geriatrics).[57] Our findings show that exercise interventions improve functional ability and physical performance at discharge, also providing benefits on the middle-term (1-3 months post-discharge). A graphical abstract of this study is shown in Figure 6.

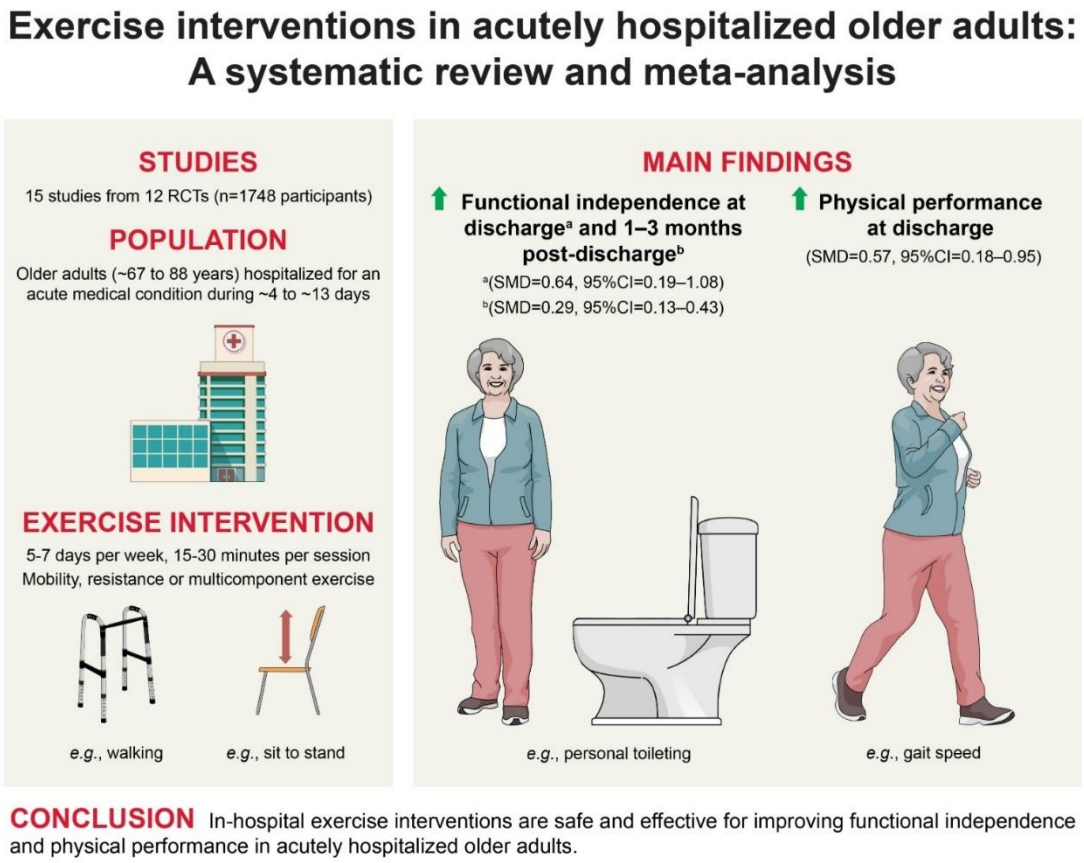


Figure 6. Summary of the effects of physical exercise interventions on the functional status of acutely hospitalized older adults.

Ageing Research Reviews 61 (2020) 101076

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Effects of exercise interventions on the functional status of acutely hospitalised older adults: A systematic review and meta-analysis

Pedro L. Valenzuela[a], Javier S. Morales[b], Adrián Castillo-García[c], Jennifer Mayordomo-Cava[d,e,f], Antonio García-Hermoso[g,h], Mikel Izquierdo[f,i], José A. Serra-Rexach[d,e,f,j], Alejandro Lucia[b,f,k,*]

[a] Department of Systems Biology, University of Alcalá, Madrid, Spain
[b] Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain
[c] Fissac – Physiology, Health and Physical Activity, Madrid, Spain
[d] Geriatric Department, Hospital Gregorio Marañón, Madrid, Spain
[e] Instituto de Investigación Sanitaria, Hospital Gregorio Marañón, Madrid, Spain
[f] Biomedical Research Networking Center on Frailty and Healthy Aging (CIBERFES), Madrid, Spain
[g] Navarrabiomed, Complejo Hospitalario de Navarra (CHN), Universidad Pública de Navarra (UPNA), IdiSNA, Pamplona, Navarra, Spain
[h] Laboratorio de Ciencias de la Actividad Física, el Deporte y la Salud, Universidad de Santiago de Chile, Santiago, Chile
[i] Department of Health Sciences, Public University of Navarra, Pamplona, Spain
[j] Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain
[k] Research Institute of the Hospital 12 de Octubre ('imas12'), Madrid, Spain

ARTICLE INFO

Keywords:
acute hospitalisation
physical exercise
hospital-associated disability
elderly
geriatric

ABSTRACT

Background: Acute hospitalisation can have adverse effects in older adults, notably functional decline. We aimed to summarize evidence on the effects of exercise interventions in acutely hospitalised older adults.
Methods: Relevant articles were systematically searched (PubMed, Web of Science, Rehabilitation & Sports Medicine Source, and EMBASE) until 19th March 2020. Randomized controlled trials (RCTs) of in-hospital exercise interventions *versus* usual care conducted in older adults (> 60yrs) hospitalised for an acute medical condition were included. Methodological quality of the studies was assessed with the PEDro scale. Primary outcomes included functional independence and physical performance. Intervention effects were also assessed for other major outcomes (length of hospital stay, incidence of readmission, and mortality). A meta-analysis was conducted when ≥3 studies analysed the same outcome.
Results: Fifteen studies from 12 RCTs (n = 1748) were included. Methodological quality of the studies was overall high. None of the studies reported any adverse event related to the intervention. Exercise interventions improved functional independence at discharge (standardized mean difference [SMD] = 0.64, 95% confidence interval = 0.19–1.08) and 1–3 months post-discharge (SMD = 0.29, 95%CI = 0.13–0.43), as well as physical performance (SMD = 0.57, 95%CI = 0.18–0.95). No between-group differences were found for length of hospital stay or risk of readmission or mortality (all $p > 0.05$).
Conclusions: In-hospital supervised exercise interventions seem overall safe and effective for improving – or attenuating the decline of – functional independence and physical performance in acutely hospitalised older adults. The clinical relevance of these findings remains to be confirmed in future research.

1. Introduction

Periods of hospitalisation as a consequence of acute medical illness are associated with several negative health consequences in older adults, even when the illness that necessitated the hospitalisation is successfully treated. Indeed, approximately one-third of older adults experience the so-called hospital-associated functional decline (HAFD) or hospitalisation-associated disability (defined as the loss of the ability to perform one or more basic activities of daily living [ADL]) (Loyd et al., 2019), which is associated with an increased risk of disability, institutionalisation and mortality (Boyd et al., 2008; Fortinsky et al., 1999; Inouye et al., 1998). Hospitalisation periods are also associated with an increased risk of cognitive decline and dementia (Ehlenbach et al., 2010). Thus, the development of strategies aiming at reducing the adverse effects of acute hospitalisation in older patients should be a priority (Covinsky et al., 2011).

* Corresponding author at: European University of Madrid, Calle Tajo, s/n, 28670, Villaviciosa de Odón, Madrid, Spain.
E-mail address: alejandro.lucia@universidadeuropea.es (A. Lucia).

https://doi.org/10.1016/j.arr.2020.101076
Received 20 March 2020; Received in revised form 14 April 2020; Accepted 18 April 2020
Available online 21 April 2020

The generally low levels of physical activity performed by hospitalised older adults seem to play a major role in the negative health consequences associated with hospitalization (Agmon et al., 2017; Pavon et al., 2019; Zisberg et al., 2011). Hospitalised older adults spend most of the time in bed even if they are able to walk independently (Brown et al., 2009), and nearly 75% of them do not walk at all during hospitalisation (Callen et al., 2004). It has been proposed that exercise interventions might be a safe and effective strategy to enhance functional status in hospitalised older patients (*e.g.,* rehabilitation programs in medically stable geriatric patients) (Bachmann et al., 2010; Heldmann et al., 2019; Kosse et al., 2013; Martínez-Velilla et al., 2016). For instance, meta-analytical evidence supports the benefits of exercise interventions on the functional status of medically stable patients (*i.e.*, in the post-acute or rehabilitation setting) and on other clinical outcomes such as risk of nursing home admission and mortality (Bachmann et al., 2010; McKelvie et al., 2018). There is also evidence of a benefit of exercise interventions on functional independence and physical performance in older adults admitted for an acute medical condition (Martínez-Velilla et al., 2019; Ortiz-Alonso et al., 2020; Sáez de Asteasu et al., 2019a) and some qualitative reviews have summarized these findings (Kanach et al., 2018; Martínez-Velilla et al., 2016). However, to our knowledge there is no meta-analytic evidence supporting the effectiveness of in-hospital exercise interventions for the improvement of functional status in this patient population, or for their effect on other major outcomes such as length of hospital stay, incidence of readmission, or mortality.

The present systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to summarize evidence on the effects of exercise interventions in acutely hospitalised older adults compared with usual care, with a particular focus on functional independence and physical performance, as well as on other clinical outcomes including length of hospital stay, incidence of readmission, and mortality.

2. Methods

The conduct and reporting of the present systematic review and meta-analysis conform to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

2.1. Systematic search

Relevant English-language articles were identified by title and abstract in the electronic databases PubMed, Web of Science, Rehabilitation & Sports Medicine Source, and EMBASE (all available documents until 19th March 2020) using the following strategy: ("older adults" OR "older patients" OR elderly OR elders OR geriatric* OR "very old" OR eldest OR oldest OR frail OR senior OR octogenarian OR nonagenarian OR centenarian) AND (hospital* OR "acute care" OR inpatient) AND (exercise* OR "physical therapy" OR rehabilitation OR training OR mobilization OR ambulat*) AND (random* OR control* OR "usual care"). The electronic search was supplemented with a manual review of reference lists from relevant publications to locate additional publications. Gray literature (*e.g.,* abstracts, conference proceedings and editorials) was excluded.

2.2. Study selection and data extraction

Two authors (J.S.M. and J.M-C) independently performed the systematic search, and eventual disagreements were resolved through discussion with a third author (P.L.V.). Citations were first retrieved and preliminarily screened by title and abstract, and the full-texts of those studies that met the inclusion criteria were assessed. Each author provided a separate list with the studies selected at each stage, as well as with those to be finally included in the review. Studies were eligible for inclusion if they met all following criteria: *a)* were RCTs; *b)* were conducted in older adults (age > 60 years) hospitalised for an acute condition (*e.g.*, mainly cardiovascular complications such as heart failure, and pulmonary complications such as exacerbations of chronic obstructive pulmonary disease and pneumonia); *c)* had a control group of patients who received usual care; *d)* had a group that received usual care and, in addition, was included in an in-hospital physical exercise intervention (exercise group); *e)* assessed at least one endpoint related to functional independence or physical performance. Studies including patients hospitalised due to orthopaedic surgery in general, knee/hip replacement, falls, stroke, or injuries (*e.g.,* fractures) as well as those conducted in a post-acute or rehabilitation unit were excluded. The control and exercise groups should receive the same treatment/conditions except for the physical exercise intervention (*e.g.,* studies assessing the effectiveness of physical exercise together with other interventions such as cognitive, nutritional or psychological ones were excluded). In order to isolate the effects of in-hospital exercise, in those studies that included a follow-up the exercise intervention should be finished at discharge.

Two authors (A.C.G. and J.S.M.) independently extracted the following data from each study: number of participants within each group, participants' characteristics, intervention characteristics, main endpoints, measurement methods, and main results. Main outcomes' data were extracted as mean and standard deviation (SD) for continuous variables or as sample size and number of events for dichotomous ones. Disagreements were resolved through discussion with a third reviewer (P.L.V.). If the aforementioned data were not available, we contacted the corresponding author of the study in question. We also contacted authors when necessary to clarify any uncertainty or to request additional data.

2.3. Quality assessment

The methodological quality of the included studies was assessed with the PEDro scale, which is based on the Delphi list (Verhagen et al., 1998). Two authors (A.C.G and J.S.M.) independently scored the studies, and disagreements were resolved through discussion with a third author (P.L.V.). A 0–10 total score was determined by counting the number of criteria satisfied by each study (see footnote in Table 1 for a brief description of criteria). Study quality was rated as poor (PEDro score ≤ 3), fair (4–5) or high (> 5).

2.4. Statistical analyses

We performed a meta-analysis when a minimum of three studies compared the effects of exercise over the control group for a given endpoint. When different studies from the same RCT assessed the same endpoint, only the larger one (*i.e.,* the one including more participants) was used for analyses. The pooled standardized mean difference (SMD, post- *minus* pre-intervention data) and odds ratio (OR) between interventions were computed together with 95% confidence interval (CI) using a random effects model. Absolute mean differences (AMD) were computed when all studies reported a given endpoint using the same units (*e.g.,* length of stay in days). A conservative correlation coefficient (Pearson's *r*-value) of 0.7 between pre- and post-intervention data was used for the computation of the within-group SD (Rosenthal, 1991), which is in line with that observed in this patient population (Ortiz-Alonso et al., 2020). Sensitivity analyses with an *r*-value of 0.2 and 0.5 were then performed when a significant result was found. Begg's test was used to determine the presence of publication bias, and the Q and I^2 statistics were used to assess heterogeneity across studies. The level of significance was set at 0.05. All statistical analyses were performed using the statistical software package Comprehensive Meta-analyis 2.0 (Biostat; Englewood, NJ).

Table 1
Characteristics of the included studies

Study	Sample demographics (n, sex, average age)	Exercise Intervention	Endpoints	Main results
Blanc-Bisson et al. (2008)	- EXP: n = 38 patients (13 female), 86 years - CT: n = 38 patients (8 female), 85 years	5 days/week, twice a day, 30 min/session. Exercises for crural triceps, legs and pelvis (10 repetitions)	- **Functional assessment:** ADL function (Katz index) and handgrip strength. - **Nutritional assessment**: energy and protein intakes. - **Anthropometry:** calf and arm circumference; triceps skin fold; and BMI.	- ↑ protein intake. - No differences in the remaining outcomes.
Braun et al. (2019)	- EXP: n = 17 patients (13 female), 79 years - CT: n = 18 patients (13 female), 83 years	4-5 days/week, 30 min/session. Strengthening (*e.g.,* heel raises, sit-to-stand, stair-walking), balance, and endurance/walking exercises. Supervised.	- **Functional assessment:** 6MWD, TUG test, gait speed. - **Mobility assessment:** DEMMI, HABAM, FAC. **Others**: FES-I.	- No differences in any outcome.
Brown et al. (2016)	- EXP: n = 50 patients (2 female), 74 years - CT: n = 50 patients (1 female), 73 years	7 days/week, twice a day, 15–20 min/session. Mobility protocol in which participants began with assisted sitting, then standing, shifting, stepping in place, and then ambulation as tolerated with assistance. Supervised.	- **Functional assessment:** ADL function (Katz index). - **Mobility assessment**: LSA. - **Clinical assessment:** length of hospital stay.	- ↑ LSA score at 1-month after hospitalisation. - No differences in the remaining outcomes.
Hu et al. (2020)	- EXP: n = 50 patients (27 female), 76 years - CT: n = 50 patients (25 female), 77 years	7 days/week, one to three times per day, up to 30 min/day. Individually tailored, mostly including mobility exercises (from mini-pedal bicycling in supine or sitting position, to ambulation training with or without assistance for those who are able to stand independently). Supervised.	- **Functional assessment:** ADL function (Katz index), lower-limb performance (TUG test) and handgrip strength. - **Quality of life:** EQ-5D. - **Clinical assessment:** length of stay	- ↑ TUG performance. - ↑ Handgrip strength. - ↑ EQ-5D at 3-month after hospitalisation. - No differences in the remaining outcomes.
Jones et al. (2006)	- EXP: n = 80 patients (43 female), 82 years - CT: n = 80 patients (49 female), 83 years	7 days/week, twice a day, ~20 min/session. Exercises focused on improving strength, balance and functional exercises. Supervised.	- **Functional assessment:** ADL function (modified Barthel index) and lower-limb performance (TUG test). - **Clinical assessment:** length of hospital stay, discharge destination.	- ↑ ADL function in those patients with low baseline functional ability. - ↑ TUG performance. - No differences in the remaining outcomes.
Killey & Watt (2006)	- EXP: n = 27 patients (female participants, not specified), 84 years - CT: n = 28 patients (female participants, not specified), 83 years	7 days/week, twice a day. Walking protocol. Supervised.	- **Functional assessment:** ADL function (Barthel index) and distance able to be walked. - **Exercise self-efficacy:** SEE scale.	- ↑ ADL function. - ↑ distance able to be walked. - No differences in SEE scale.
Martínez-Velilla et al. (2019)	- EXP: n = 185 patients (100 female), 88 years - CT: n = 185 patients (109 female), 87 years	5–7 days/week, twice a day, 15–20 min/session. Morning sessions included moderate-intensity resistance (squats rising from a chair, leg press, bilateral knee extension, and seated bench press [2–3 sets, 8–10 repetitions, 30–60% 1-RM]), balance, and walking exercises. Evening sessions included knee extension and flexion, hip abduction (with light loads), and walking exercises. Supervised.	- **Functional assessment:** ADL function (Barthel index); SPPB scale; handgrip strength. - **Cognitive assessment**: MMSE; GDS; and CAM. - **Quality of life:** EQ-5D. - **Clinical assessment:** length of stay and falls during hospitalisation; transfer after discharge; and readmission rate; and mortality up to 3 months after discharge.	- ↑ ADL function and SPPB score, and handgrip strength. - ↑ MMSE and GDS score. - ↑ EQ-5D. - No differences in the remaining outcomes.
McCullagh et al. (2020)	- EXP: n = 95 patients (39 female), 80 years - CT: n = 95 patients (61 female), 82 years	5 day/week, twice a day, up to 20 min/session. Including strength (squat rising from a chair, heel raises), walking and balance exercises. Supervised.	- **Functional assessment:** SPPB scale. - **Mobility assessment**: Number of steps. - **Quality of life:** EQ-5D. - **Clinical assessment:** length of stay, and falls, readmission rate, and mortality up to 3 months after discharge.	- ↑ SPPB. - ↑ EQ-5D at follow up. - No differences in the remaining outcomes.
Ortiz-Alonso et al. (2020)	- EXP: n = 143 patients (86 female), 88 years - CT: n = 125 patients (68 female), 88 years	5 day/week, one to three times per day, ~20 min/session. Rising from a seated to an upright position (1–3 sets of 10 repetitions) and supervised walking exercises (3–10 minutes). Supervised.	- **Functional assessment:** ADL function (Katz index); SPPB scale. - **Mobility assessment**: FAC. - **Clinical assessment:** length of stay, and falls, readmission rate, and mortality up to 3 months after discharge.	- ↓ Incidence of HAD from admission to discharge and 3 months later. - No differences in the remaining outcomes.
Sáez de Asteasu et al. (2019a)	- EXP: n = 185 patients (100 female), 88 years - CT: n = 185 patients (109 female), 87 years	5–7 days/week, twice a day, 15–20 min/session. Morning sessions included moderate-intensity resistance (squats rising from a chair, leg press, bilateral knee extension, and seated bench press [2–3 sets, 8–10 repetitions, 30–60% 1-RM]), balance,	- **Cognitive assessment**: 6-meter dual-task GVT; TMT-A; MMSE; and verbal fluency test.	- ↑ verbal and arithmetic GVT, TMT-A, MMSE, and verbal fluency score.

(*continued on next page*)

Table 1 (*continued*)

Study	Sample demographics (n, sex, average age)	Exercise Intervention	Endpoints	Main results
		and walking exercises. The evening sessions included knee extension and flexion, hip abduction (with light loads), and walking exercises. Supervised.		
Sáez de Asteasu et al. (2019b)	- EXP: n = 65 patients (32 female), 88 years - CT: n = 65 patients (32 female), 86 years	Same as above.	- **Functional assessment:** SPPB scale; 5STS, lower-limb strength (bilateral leg press 1RM); and PW50. - **Cognitive assessment**: 6-meter dual-task GVT and dual-task gait.	- ↑ SPPB and 5STS score, lower-limb strength, and PW50. - ↑ verbal and arithmetic GVT score.
Sáez de Asteasu et al. (2020)	- EXP: n = 185 patients (100 female), 88 years - CT: n = 185 patients (109 female), 87 years	Same as above.	- **Functional assessment:** lower- and upper-limb strength (1RM for bilateral leg press, chest-press and knee extension; and maximal isometric strength for knee extensors and hip flexors), and power output at submaximal loads.	- ↑ upper- and lower-limb strength. - ↑ power output.
Siebens et al. (2000)	- EXP: n = 149 patients (88 female), 79 years - CT: n = 151 patients (94 female), 78 years	Twice a day. Flexibility, resistance (shoulder blade pinch, arm press, biceps curl, arm circles, tummy strengthener, leg lifts, toe/heel raises and leg swings [5–10 repetitions]), and walking (60–80% HR_{max}) exercises. Supervised.	- **Functional assessment:** FIM; IADL; and the National Health Interview Survey Physical Activity Scale. - **Quality of Life:** RAND General Health Scale. - **Clinical assessment:** length of stay and mortality.	- ↑ IADL score at 1-month after hospitalisation. - No differences in the remaining outcomes.
Torres-Sánchez et al. (2017)	- EXP: n = 29 patients (7 female), 76 years - CT: n = 29 patients (9 female), 72 years	7 days/week Cycling protocol using a pedal exerciser (< 6 in the Borg scale). Supervised.	- **Functional assessment:** lower-limb strength; OLS and STS test. - **Physical activity levels**: SenseWear Armband.	- ↑ lower-limb strength and OLS test. - ↑ steps per day. - No differences in the remaining outcomes.
Troosters et al. (2010)	- EXP: n = 17 patients (4 female), 67 years - CT: n = 19 patients (5 female), 69 years	7 days/week Resistance exercises (knee extension [3 sets, 8 repetitions, 70% 1-RM]) Supervised.	- **Functional assessment:** lower-limb strength and 6MWD. - **Haematological measures:** white blood cell count; CRP; testosterone; and IGF-1. - **Clinical assessment:** length of stay and readmission rate.	- ↑ lower-limb strength. - No differences in the remaining outcomes.

Abbreviations: ADL, activities of daily living; BMI, body mass index; CAM, Confusion Assessment Method; CRP, C-reactive protein; CT, control group; DEMMI, de Morton Mobility Index; EQ-5D, EuroQol–5 Dimension; EXP, experimental group; FAC, Functional Ambulatory Categories; FES-I, Falls Efficacy Scale-International; FIM, Functional Independence Measure; GDS, Geriatric Depression Scale; GVT, Gait Velocity Test; HABAM, Hierarchical Assessment of Balance and Mobility; HAD, hospital-associated disability; HR, maxmaximum heart rate; IADL, Instrumental Activities of Daily Living; IGF-1, insulin-like growth factor-1; LSA, the University of Alabama at Birmingham Study of Aging Life-Space Assessment; Mini-Cog, Mini-Cognitive Assessment; MMSE, Mini-Mental State Examination; N/R, not reported; OLS, one-leg stance; PW50, leg power at an intensity of 50% of 1RM; RM, repetition maximum; SEE, Self-Efficacy for Exercise; SPPB, Short Physical Performance Battery; STS, sit-to-stand; TMT-A, Trail Making Test Part A; TUG, timed up and go test; 6MWD, 6-minute walk distance.

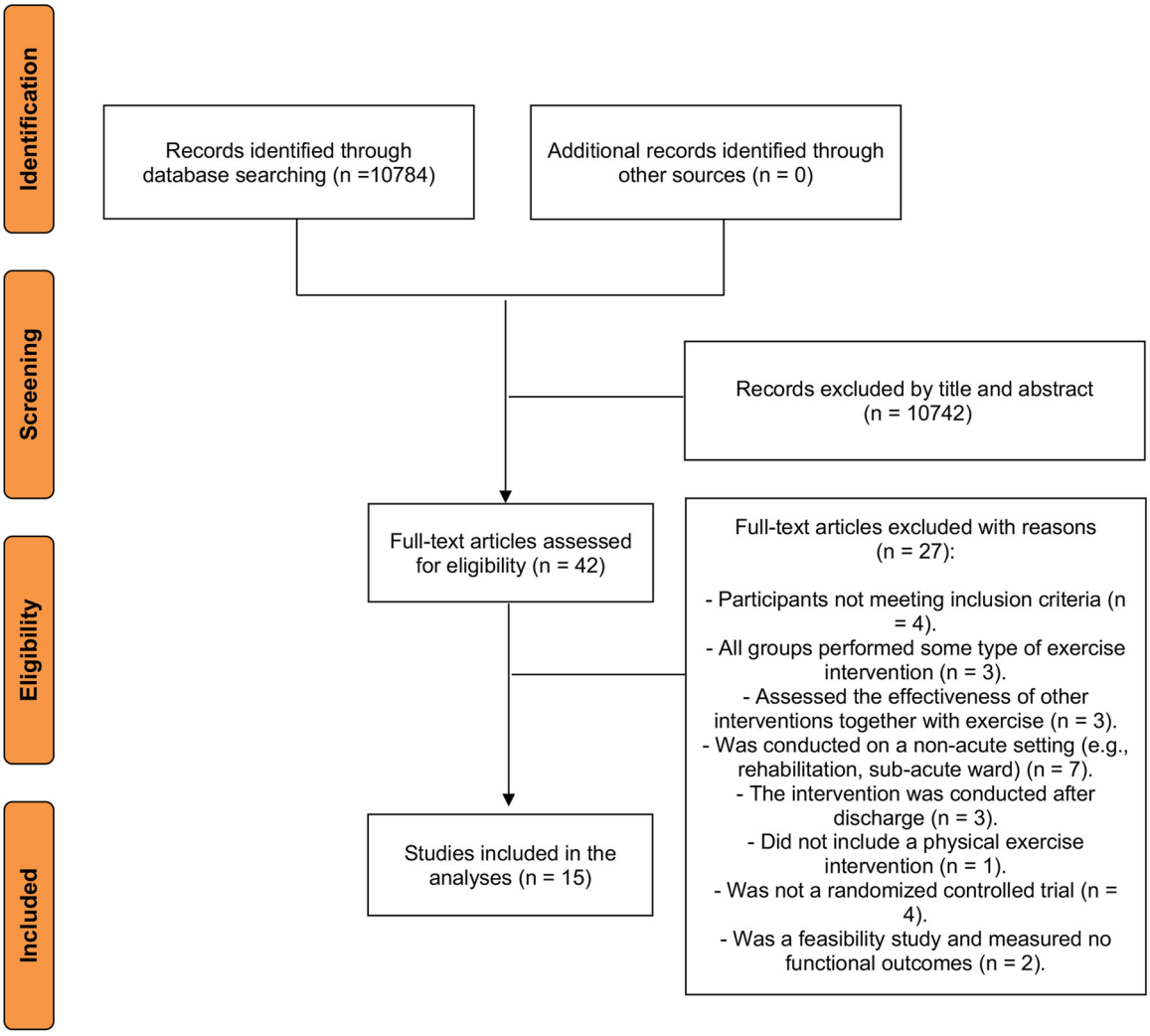


Fig. 1. Flow chart of literature search.

3. Results

3.1. Studies' selection

From the retrieved articles, 15 studies from 12 RCTs including 2618 patients were included in the systematic review (Fig. 1) (Blanc-Bisson et al., 2008; Braun et al., 2019; Brown et al., 2016; Hu et al., 2020; Jones et al., 2006; Killey and Watt, 2006; Martínez-Velilla et al., 2019; McCullagh et al., 2020; Ortiz-Alonso et al., 2020; Sáez de Asteasu et al., 2019b, 2019a, 2020; Siebens et al., 2000; Torres-Sánchez et al., 2017; Troosters et al., 2010). The characteristics of the included studies are summarized in Table 1. Three studies (Sáez de Asteasu et al., 2019a, 2019b, 2020) were secondary analyses of another RCT (Martínez-Velilla et al., 2019), and thus only the original RCT was used to calculate the total number of subjects (1748 patients after removing secondary analyses).

3.2. Quality assessment and publication bias

The quality of the included RCTs was overall high (median PEDro score = 7, range 3–8; Table 2). Two studies were deemed to have poor methodological quality (Blanc-Bisson et al., 2008; Killey and Watt, 2006), two had fair quality (Ortiz-Alonso et al., 2020; Troosters et al., 2010), and the remainder were considered to present a high quality (Brown et al., 2016; Hu et al., 2020; Jones et al., 2006; Martínez-Velilla et al., 2019; McCullagh et al., 2020; Sáez de Asteasu et al., 2020, 2019b, 2019a; Siebens et al., 2000; Torres-Sánchez et al., 2017).

3.3. Participants' characteristics

The included RCTs involved between 35 and 370 participants (median = 100) whose average age ranged between 67 and 88 years (Table 1). All studies included both male and female participants. Most studies included participants hospitalised for different medical conditions (*e.g.,* respiratory, cardiovascular, renal/urologic, central nervous system or digestive conditions). However, two studies (Torres-Sánchez et al., 2017; Troosters et al., 2010) were solely conducted in patients admitted for an exacerbation of chronic obstructive pulmonary disease. The average length of stay was between 4 and 13 days (median = 8).

3.4. Interventions' characteristics

Exercise interventions were supervised, lasted 15–30 minutes, and were performed 5–7 days per week. In nine of the 12 RCTs, interventions were performed more than once daily (up to three times per day). Four RCTs included only mobility/endurance exercises (*e.g.,* walking, pedalling) (Brown et al., 2016; Hu et al., 2020; Killey and Watt, 2006; Torres-Sánchez et al., 2017), two RCTs included only resistance exercises (*e.g.,* isometric exercises, dynamic exercises against an external load) (Blanc-Bisson et al., 2008; Troosters et al., 2010), and the remaining six RCTs applied a multicomponent intervention including both walking and resistance exercises (Braun et al., 2019; Jones et al.,

Table 2
Quality of the studies included in the systematic review

Items Authors (year)	1	2	3	4	5	6	7	8	9	10	11	Total Score*
Blanc-Bisson et al. (2008)	+	-	-	+	-	-	-	-	+	+	-	3
Braun et al. (2019)	+	+	+	+	-	-	+	+	+	+	+	8
Brown et al. (2016)	+	+	+	+	-	-	+	+	+	+	+	8
Hu et al. (2020)	+	+	+	+	-	-	-	+	-	+	+	6
Jones et al. (2006)	+	+	-	-	-	-	+	+	+	+	+	6
Killey & Watt (2006)	+	-	-	+	-	-	-	-	?	+	+	3
Martínez-Velilla et al. (2019)	+	+	+	+	-	-	+	+	+	+	+	8
McCullagh et al. (2020)	+	+	+	+	-	-	+	+	+	+	+	8
Ortiz-Alonso et al. (2020)	+	+	-	-	-	-	-	+	-	+	+	4
Sáez de Asteasu et al. (2019a)	+	+	+	+	-	-	+	+	+	+	+	8
Sáez de Asteasu et al. (2019b)	+	+	+	+	-	-	+	+	+	+	+	8
Sáez de Asteasu et al. (2020)	+	+	+	+	-	-	+	+	+	+	+	8
Siebens et al. (2000)	+	+	-	+	-	-	+	+	+	+	+	7
Torres-Sánchez et al. (2017)	+	+	+	+	-	-	+	+	+	+	+	8
Troosters et al. (2010)	+	+	+	-	-	-	-	-	?	+	+	4

Column numbers correspond to the following criteria on the PEDro scale:
[1] - eligibility criteria were specified
[2] - subjects were randomly allocated to groups (or, in a crossover study, subjects were randomly allocated an order in which treatments were received)
[3] - allocation was concealed
[4] - groups were similar at baseline
[5] - subjects were blinded
[6] - therapists who administered the treatment were blinded
[7] - assessors were blinded
[8] - measures of key outcomes were obtained from more than 85% of subjects
[9] - data were analysed by intention to treat
[10] - statistical comparisons between groups were conducted
[11] - point measures and measures of variability were provided.
*A total score out of 10 is determined from the number of criteria that are satisfied, except that scale item 1 is not used to generate the total score.
[+] Indicates the criterion was clearly satisfied; - indicates that it was not;? indicates that it is not clear if the criterion was satisfied.

2006; Martínez-Velilla et al., 2019; McCullagh et al., 2020; Ortiz-Alonso et al., 2020; Siebens et al., 2000).

3.5. Endpoints

3.5.1. Adverse events

Nine of the 12 included RCTs registered the incidence of adverse events related to the exercise intervention (*e.g.,* asthma exacerbation, dizziness, falls, musculoskeletal injuries), and none reported any adverse event (Braun et al., 2019; Brown et al., 2016; Jones et al., 2006; Killey and Watt, 2006; Martínez-Velilla et al., 2019; McCullagh et al., 2020; Ortiz-Alonso et al., 2020; Siebens et al., 2000; Torres-Sánchez et al., 2017).

3.5.2. Functional independence

Eight studies assessed patients' functional independence on instrumental (Siebens et al., 2000) or basic ADLs using either the Katz (Blanc-Bisson et al., 2008; Brown et al., 2016; Hu et al., 2020; Ortiz-Alonso et al., 2020) or Barthel index (Killey and Watt, 2006; Jones et al., 2006; Martínez-Velilla et al., 2019). Of these, seven (Blanc-Bisson et al., 2008; Brown et al., 2016; Hu et al., 2020; Jones et al., 2006; Killey and Watt, 2006; Martínez-Velilla et al., 2019; Ortiz-Alonso et al., 2020) assessed patients' ability to independently perform ADL at admission and discharge – although data from two of them (Blanc-Bisson et al., 2008; Jones et al., 2006) could not be obtained despite contacting the authors. Overall, exercise interventions improved ADL function over usual care (n = 870, SMD = 0.64, p = 0.005, Fig. 2A), with low heterogeneity (Q = 6.489, I^2 = 38%) and no sign of publication bias (p = 0.403). This effect remained significant in sensitivity analyses (r = 0.5, SMD = 0.50, p = 0.007; r = 0.2, SMD = 0.39, p = 0.010). Of note, one study (Jones et al., 2006) found an increased ADL function after the exercise intervention only in those patients with a lower baseline functional status.

Four studies (Brown et al., 2016; Hu et al., 2020; Ortiz-Alonso et al., 2020; Siebens et al., 2000) compared ADL function after hospitalisation (1–3 months after discharge) to that at baseline (*e.g.,* 2 weeks before admission). Pooled analyses showed that exercise improved ADL function over usual care (n = 744, SMD = 0.28, p < 0.001, Fig. 2B), with no evidence of heterogeneity (Q = 2.639, I^2 = 0%) or publication bias (p = 0.500). This effect remained in sensitivity analyses (r = 0.5, SMD = 0.22, p = 0.005; r = 0.2, SMD = 0.18, p = 0.023).

3.5.3. Physical performance

Ten studies (Braun et al., 2019; Hu et al., 2020; Jones et al., 2006; Killey and Watt, 2006; Martínez-Velilla et al., 2019; McCullagh et al., 2020; Ortiz-Alonso et al., 2020; Sáez de Asteasu et al., 2019b; Torres-Sánchez et al., 2017; Troosters et al., 2010) assessed endpoints related to physical performance (*i.e.,* short physical performance battery [SPPB], 5-sit-to-stand [5STS] test, timed up and go [TUG] test, 6-minute walking distance [6MWD] test, distance able to be walked). After removing sub-studies (Sáez de Asteasu et al., 2019b), results showed that exercise resulted in an enhanced physical performance (n = 1052, SMD = 0.57, p = 0.004, Fig. 2C), with no signs of heterogeneity (Q = 4.869, I^2 = 0%) or publications bias (p = 0.382). This effect remained significant in sensitivity analyses (r = 0.5, SMD = 0.45, p = 0.004; r = 0.2, SMD = 0.36, p = 0.005). Data from two studies (Jones et al., 2006; Troosters et al., 2010), which also found an increased physical performance (as measured with the TUG and 6MWD tests) with the exercise intervention, could not be obtained and therefore these studies were not included in the analysis.

Six studies (Blanc-Bisson et al., 2008; Martínez-Velilla et al., 2019; Sáez de Asteasu et al., 2020, 2019b; Torres-Sánchez et al., 2017; Troosters et al., 2010) assessed markers of maximal voluntary muscle strength. Four studies (Sáez de Asteasu et al., 2020, 2019b; Torres-Sánchez et al., 2017; Troosters et al., 2010) assessed different markers of lower and upper-limb maximal voluntary strength (*i.e.,* isometric strength or 1-repetition maximum [1-RM]), and all of them found a beneficial effect of exercise over usual care. However, these results

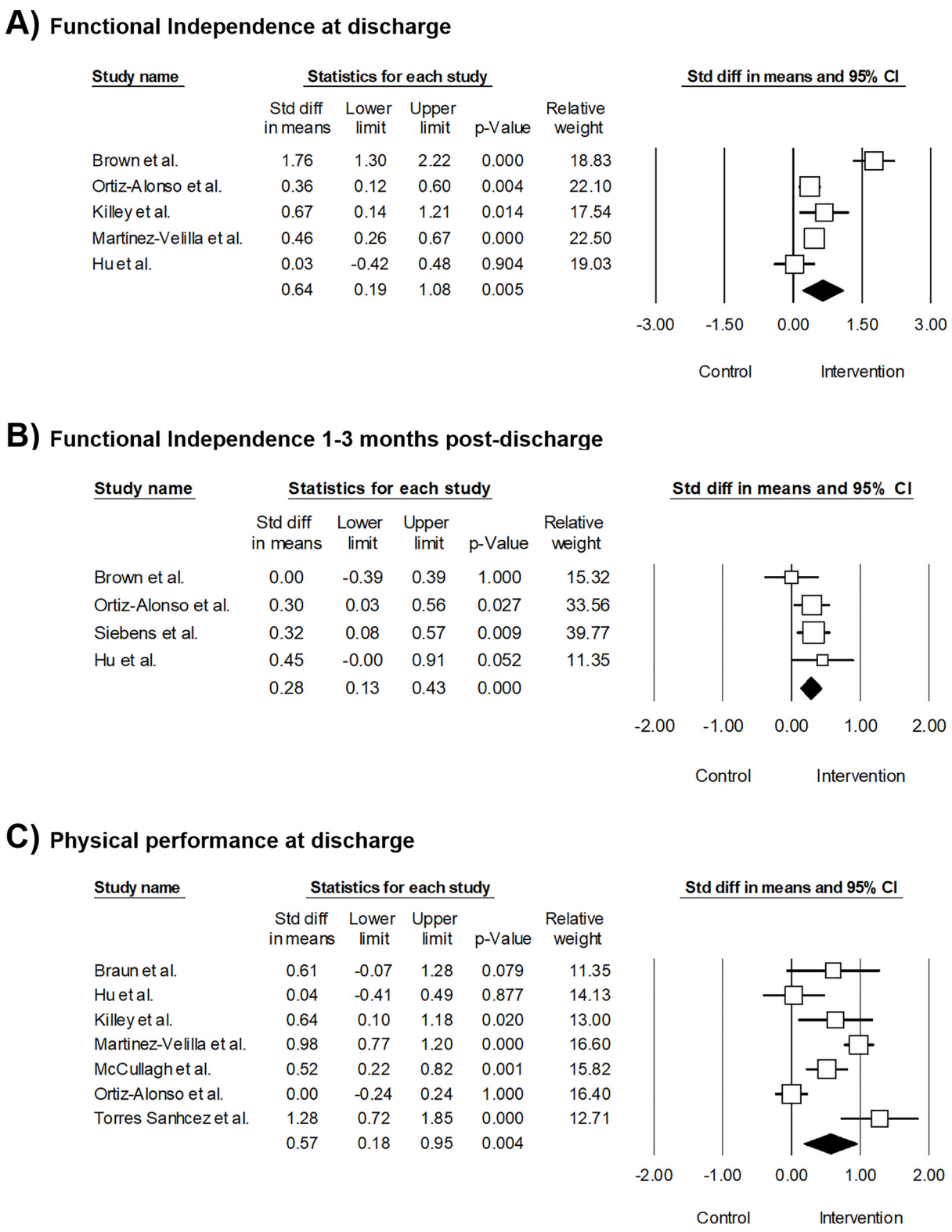


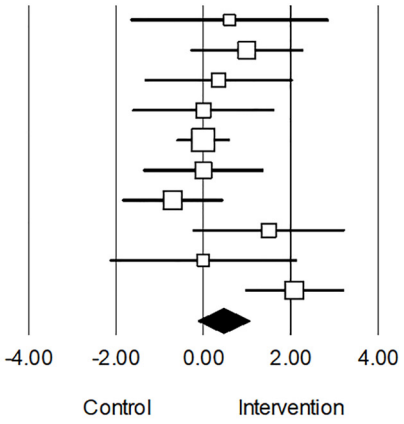
Fig. 2. Effects of exercise interventions in hospitalised older adults on functional independence (the ability to independently perform activities of daily living) measured at discharge (panel **A**) and 1–3 months post-discharge (panel **B**), as well as on physical performance measured at discharge (panel **C**).

could not be meta-analysed because the data of one study (Troosters et al., 2010) were not available, and two pertained to the same RCT (Sáez de Asteasu et al., 2020, 2019b). Three studies assessed handgrip strength (Blanc-Bisson et al., 2008; Hu et al., 2020; Martínez-Velilla et al., 2019), of which two found a significant beneficial effect of the exercise intervention (Hu et al., 2020; Martínez-Velilla et al., 2019).

Two studies from the same original RCT reported benefits on the muscle power output generated with leg-press exercise at submaximal loads (30 to 75% of 1-RM) as well as in the 5STS test (Sáez de Asteasu et al., 2020, 2019b).

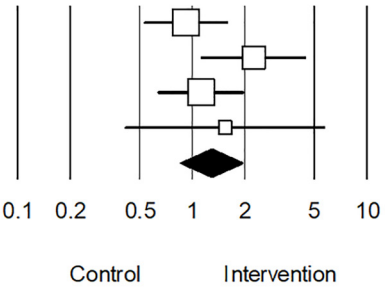
A) Length of hospital stay

Study name	Difference in means	Lower limit	Upper limit	p-Value	Relative weight
Braun et al.	0.60	-1.66	2.86	0.603	5.20
Brown et al.	1.00	-0.29	2.29	0.130	10.99
Hu et al.	0.35	-1.35	2.05	0.686	7.90
Jones et al.	0.00	-1.62	1.62	1.000	8.39
Martinez-Velilla et al.	0.00	-0.60	0.60	1.000	19.02
McCullagh et al.	0.00	-1.38	1.38	1.000	10.26
Ortiz-Alonso et al.	-0.70	-1.85	0.45	0.233	12.37
Siebens et al.	1.50	-0.24	3.24	0.090	7.67
Troosters et al.	0.00	-2.14	2.14	1.000	5.67
Torres-Sánchez et al.	2.09	0.96	3.22	0.000	12.55
	0.46	-0.12	1.04	0.123	



B) Risk of re-hospitalisation

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Martinez-Velilla et al.	0.92	0.53	1.61	0.778	33.70
McCullagh et al.	2.25	1.13	4.49	0.021	25.04
Ortiz-Alonso et al.	1.12	0.64	1.98	0.689	32.63
Troosters et al.	1.55	0.41	5.78	0.516	8.64
	1.29	0.86	1.93	0.226	



C) Risk of mortality

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Martinez-Velilla et al.	1.25	0.65	2.42	0.504	33.48
McCullagh et al.	0.38	0.13	1.12	0.080	19.97
Ortiz-Alonso et al.	0.41	0.15	1.13	0.086	21.81
Siebens et al.	1.01	0.41	2.51	0.975	24.73
	0.74	0.40	1.35	0.320	

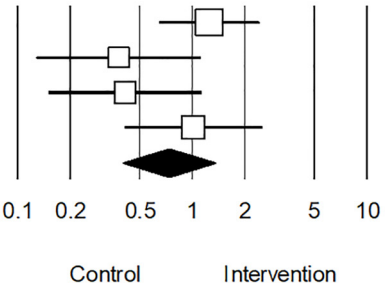


Fig. 3. Effects of exercise interventions in hospitalised older adults on the length of hospital stay (panel **A**) and on the risk of re-hospitalisation 3–6 months after discharge (panel **B**) and mortality 1–3 months after discharge (panel **C**).

3.5.4. Cognitive and psychological measures

Three studies (pertaining to the same RCT) (Martínez-Velilla et al., 2019; Sáez de Asteasu et al., 2019b, 2019a) assessed different cognition-related measures. The exercise intervention proved beneficial for enhancing cognition (executive function and verbal fluency domains) as measured by the mini-mental state examination, performance on a dual-task gait velocity test, the Trail Making Test Part A, and a verbal fluency test (Martínez-Velilla et al., 2019; Sáez de Asteasu et al., 2019b, 2019a). Benefits were also observed on the incidence of depression symptoms (as measured with the Yesavage Geriatric Depression Scale) compared with usual care, but no benefits were reported for incident delirium (Martínez-Velilla et al., 2019).

Three studies (Hu et al., 2020; Martínez-Velilla et al., 2019; McCullagh et al., 2020) assessed quality of life at discharge by means of the EuroQol–5 Dimension visual analogue scale (VAS), and their pooled analyses showed no significant benefits of the exercise intervention compared with usual care (n = 636, AMD = 6.4 points, 95%CI = -2.1–14.9, p = 0.138; Q = 1.335, I^2 = 0%, Begg's p = 0.500). One of these studies found benefits during the follow-up, but not at discharge (McCullagh et al., 2020), and another found benefits on the EuroQol–5 questionnaire, but not on the VAS (Hu et al., 2020). Another study (Siebens et al., 2000) found no differences between groups in overall health perception measured by means of the RAND General Health Scale.

3.5.5. Physical activity levels and mobility-related measures

Two studies (McCullagh et al., 2020; Torres-Sánchez et al., 2017) reported that the exercise intervention resulted in an increased number of steps (measured through accelerometry) per day during hospitalisation compared with the control group. Another study (Brown et al., 2016) observed that the exercise intervention resulted in higher scores in the life-space assessment (assessed by means of the University of Alabama at Birmingham Life-Space Assessment, which measures community mobility) after hospitalisation (*i.e.*, 1 month after discharge) compared with the control group. However, no differences were reported between groups for basic ambulation (*i.e.*, the proportion of participants who required assistance, used a cane or walker, or could walk independently, assessed by means of the Functional Independence Measure), community mobility (*i.e.,* frequency of leaving the neighbourhood), or for the National Health Interview Survey Physical Activity Scale in another study (Siebens et al., 2000). Similarly, one study (Ortiz-Alonso et al., 2020) observed no benefits of an exercise intervention over the control group on the Functional Ambulation Category (FAC), and another pilot study (Braun et al., 2019) found no significant benefits on FAC, the de Morton Mobility Index, or the Hierarchical Assessment of Balance and Mobility.

3.5.6. Blood variables

One study (Troosters et al., 2010) reported reductions in inflammatory markers (*i.e.,* C-reactive protein and white blood cell counts) as well as increases in testosterone and insulin growth factor-1 from admission to discharge, with no differences between the intervention and control groups.

3.5.7. Anthropometrical variables

Only one study (Blanc-Bisson et al., 2008) analysed the effects of exercise interventions on anthropometrical variables (*i.e.,* calf and arm circumference, and triceps skin fold), finding no differences compared with the control group.

3.5.8. Length of stay

Ten studies (Braun et al., 2019; Brown et al., 2016; Hu et al., 2020; Jones et al., 2006; Martínez-Velilla et al., 2019; McCullagh et al., 2020; Ortiz-Alonso et al., 2020; Siebens et al., 2000; Torres-Sánchez et al., 2017; Troosters et al., 2010) compared the length of stay of the exercise and control groups and no overall differences were found (n = 1616, AMD = 0.46 days, p = 0.123, Fig. 3A), with little evidence of heterogeneity (Q = 16.762, I^2 = 46%) and no signs of publication bias (p = 0.186).

3.5.9. Falls

Six studies assessed falls during hospitalization (Brown et al., 2016; Jones et al., 2006; Killey and Watt, 2006; Martínez-Velilla et al., 2019; McCullagh et al., 2020; Ortiz-Alonso et al., 2020), with r pooled analysis showing no significant differences between interventions (n = 1148, OR = 1.14, 95%CI = 0.36–3.57, p = 0.82; Q = 4.75; I2 = 6.4%; Begg's p = 0.403). Two studies assessed the self-reported incidence of falls during a 3-month follow-up, with one reporting a lower incidence in the intervention group (McCullagh et al., 2020) and the other reporting no significant differences (Ortiz-Alonso et al., 2020).

3.5.10. Re-hospitalisation

Four studies (Martínez-Velilla et al., 2019; McCullagh et al., 2020; Ortiz-Alonso et al., 2020; Troosters et al., 2010) assessed the incidence of readmission during the 3–6 months post-discharge period, and no differences were found between groups (n = 863, OR = 1.29, 95%CI = 0.86-1.93, p = 0.226, Fig. 3B), with no evidence of heterogeneity (Q = 2.874, I^2 = 0%) or publication bias (p = 0.154).

3.5.11. Mortality

Four studies (Martínez-Velilla et al., 2019; McCullagh et al., 2020; Ortiz-Alonso et al., 2020; Siebens et al., 2000) assessed the incidence of mortality 1–3 months after discharge and no significant differences were found between the exercise and control groups (n = 1127, OR = 0.74, 95%CI = 0.40-1.35, p = 0.320, Fig. 3C), with no evidence of heterogeneity (Q = 2.931, I^2 = 0%) but signs of publication bias (p = 0.045).

4. Discussion

In this systematic review and meta-analysis of RCTs, in-hospital supervised exercise interventions appeared to be safe – as reflected by the lack of adverse events and of between-group differences in the incidence of falls – and effective for improving patients' functional independence and physical performance compared to usual care. In turn, no differences were observed between groups for quality of life at discharge, the length of hospital stay, or for the risk of readmission or mortality. Of note, these results were based on evidence that can be considered, on average, of high quality (*i.e.*, PEDro score ≥6 for each of the different outcomes we assessed) (Table 3). However, no meta-analytical evidence could be obtained for the benefits of exercise on muscle strength, mobility (*e.g.,* physical activity levels or ambulatory capacity), cognitive (*e.g.,* incident delirium), anthropometrical (*e.g.,* muscle mass) or blood parameters (*e.g.,* inflammatory markers).

Our finding that inpatient exercise interventions significantly enhance the ability to independently perform ADL at discharge and 1–3 months post-discharge over usual care in acutely hospitalised patients is potentially relevant, particularly given that HAFD is frequent among hospitalised older adults (Loyd et al., 2019) and has major negative consequences for patients (*e.g.,* higher risk of long-term disability, institutionalisation and mortality) and their caregivers (Covinsky et al., 2011; Valenzuela et al., 2020). Moreover, exercise resulted in a higher lower-extremity physical performance at discharge, which has proven to be a strong predictor of better outcomes (*i.e.,* lower risk of functional decline, re-hospitalisation and death) after acute hospitalisation in this patient population (Corsonello et al., 2012; Volpato et al., 2011). Overall, these results suggest that exercise might reduce the incidence of functional decline in this patient population, and reinforce the routine implementation of exercises during the acute hospitalisation of older patients.

It must be noted that although physical exercise appeared to be overall effective for the improvement of functional independence, not

Table 3
Summary of pooled results.

Outcome	Number of studies (number of participants)	Results (effect estimate [95%CI])	Studies' quality (mean PEDro score [range])
Functional independence at discharge	5 (n = 870)	SMD = 0.64 (0.19, 1.08)	6 (3, 8)
Functional independence 1-3 months post-discharge	4 (n = 744)	SMD = 0.28 (0.13, 0.43)	6 (4, 8)
Physical performance at discharge	7 (n = 1,052)	SMD = 0.57 (0.18, 0.95)	6 (3, 8)
Quality of life at discharge (EQ-5D VAS score)	3 (n = 636)	AMD = 6.4 (-2.1, 14.9)	7 (6, 8)
Length of hospital stay (days)	10 (n = 1,616)	AMD = 0.46 (-0.12, 1.04)	7 (4, 8)
Falls during hospitalization	6 (n = 1,148)	OR = 1.14 (0.36, 3.57)	6 (3, 8)
Risk of re-hospitalization 3-6 months post-discharge	4 (n = 863)	OR = 1.29 (0.86, 1.93)	6 (4, 8)
Mortality 1-3 months post-discharge	4 (n = 1,127)	OR = 0.74 (0.40, 1.35)	7 (4, 8)

Abbreviations: AMD, absolute mean difference; CI, confidence interval; EQ-5D VAS, EuroQol–5 Dimension visual analogue scale; OR, odds ratio; SMD, standardized mean difference.

all types of exercise interventions might provide the same effects. Walking and other mobility exercises have been reported as beneficial for maintaining pre-admission mobility levels and for the improvement of ADL function (Cohen et al., 2019; Killey and Watt, 2006; Padula et al., 2009). However, Brown et al. (2016) and Hu et al. (2020) found no benefits on ADL function with a program solely consisting of mobility exercises. In this regard, it has been suggested that multicomponent interventions including both mobility and strengthening exercises might provide greater benefits on functional ability (Martínez-Velilla et al., 2016), which is supported by different RCTs (Martínez-Velilla et al., 2019; Ortiz-Alonso et al., 2020; Siebens et al., 2000). Indeed, simple multicomponent interventions solely consisting of walking and rising from a chair have proven effective to decrease the incidence of HAFD in acutely hospitalised very old patients – particularly in those with the worst functional status at admission – (Ortiz-Alonso et al., 2020; Valenzuela et al., 2020), and even some passive physical strategies can be applied when participants cannot perform volitional exercise (Valenzuela et al., 2019, 2018). Several options are therefore available that might ease the routine implementation of exercise interventions in the clinical setting.

Beyond the benefits on ADL function, exercise might potentially exert several other benefits in hospitalised patients. Short disuse situations such as those elicited by hospitalisation can exacerbate the age-related deterioration that occurs in multiple organic systems (Bell et al., 2016), including loss of muscle mass and strength (Coker et al., 2015; Dirks et al., 2014; Tanner et al., 2015) as well as impairment in glucose homeostasis (Biensø et al., 2012; Dirks et al., 2016; McGlory et al., 2017; Wall et al., 2013). The inclusion of relatively little amounts of physical activity/exercise during hospitalisation might offset some of these negative adaptations (Mañas et al., 2019), but further research is needed to support this hypothesis. Preliminary evidence also suggests that exercise might be an effective strategy for the prevention of cognitive decline in hospitalised older adults (Martínez-Velilla et al., 2019; Sáez de Asteasu et al., 2019a). These benefits would be of major importance given the high risk of cognitive decline associated with hospitalisation in this patient population (Ehlenbach et al., 2010; Wilson et al., 2012). However, there is currently not enough evidence to support the benefits of exercise interventions in this regard. Moreover, further research is needed regarding the effects – whether negative or positive – of exercise interventions on other important outcomes not assessed here nor in the studies that we analysed such as pain or discomfort perception, as well as on drug side effects.

Given the observed benefits on functional independence and physical performance, it can also be hypothesized that exercise would result in a shorter hospitalisation stay, with consequent economic implications. However, none of the included studies found differences between groups for this endpoint. Moreover, no benefits were observed 1–6 months after discharge for other clinical endpoints such as readmission and mortality risk. Thus, although exercise interventions might be beneficial for the prevention of functional decline, they seem to exert no noticeable influence on other relevant clinical endpoints compared with usual care.

A major strength of the present meta-analysis is that, to our knowledge, it is the first to analyse the effects of exercise interventions in acutely hospitalised older adults. Bachman et al. (2010) did provide meta-analytical evidence on the effects of exercise interventions in older adults in the clinical setting, but patients were medically stable (including post-acute and rehabilitation units) and exercise programs were performed as a rehabilitation tool after conditions such as bone fractures. Although a recent systematic review provided a qualitative synthesis (*i.e.,* with no meta-analysis) of the effects of physical exercise for hospitalised older adults, lower-quality original studies (non-randomized or controlled trials) were included, and not only in-hospital, but also home-based and outpatient physical exercise interventions were analysed (Kanach et al., 2018). In turn, in the present meta-analysis we set strict inclusion/exclusion criteria in order to focus on acute medical conditions and to isolate the effect of in-hospital exercise per se – independently of other concomitant interventions (*e.g.,* the mobilization programs used in acute elder units).

Some limitations must however be acknowledged. The limited number of available studies and the heterogeneity found across studies in terms of included populations (*e.g.,* age, conditions) and interventions (*e.g.,* mobility exercises, multicomponent intervention) precluded us from performing sub-analyses attending to these variables. Further research is needed to compare the effectiveness of different types of exercise interventions in this patient population, as well as to corroborate whether similar beneficial effects can be found in patients with different characteristics – in terms of functional status and clinical conditions (*e.g.*, including pain, fatigue, or discomfort). Moreover, whether the benefits and safety observed here for supervised interventions also apply to non-supervised interventions remains unknown. The inconsistency in the endpoints assessed by each study (*e.g.,* functional independence, physical performance, strength) and the methods used for their assessment (*e.g.,* SPPB, TUG, 6MWD) also hindered the meta-analysis, which would be partly solved if a core-set of outcome measures was developed in this field of research. Indeed, because the included studies used different markers for the assessment of a given outcome, our meta-analysis results were presented as standardized differences, which precludes us from drawing strong conclusions on their actual clinical importance (*i.e.*, if the benefits surpass the minimal clinically important difference). Finally, data from some studies could not be obtained despite contacting the corresponding authors, and thus these studies could not be included in the quantitative analyses, which might be regarded as a potential bias.

5. Conclusions

In-hospital supervised exercise interventions appear to be safe and effective for improving – or attenuating the decline of – functional independence and physical performance in older adults hospitalised for

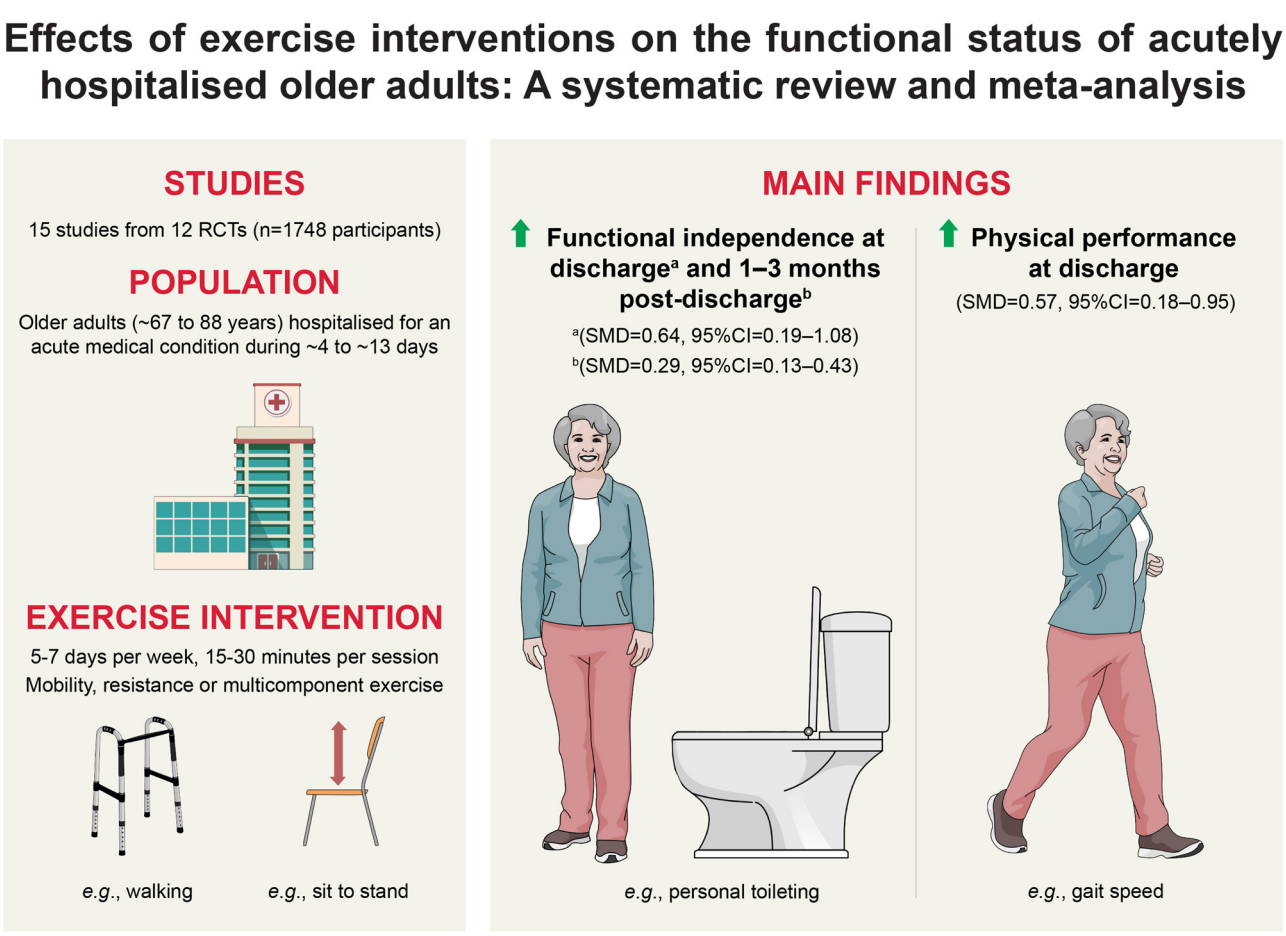


Fig. 4. Summary of study findings.

an acute medical condition (Fig. 4). However, no differences were observed compared with usual care for other major outcomes such as the length of stay, risk of readmission, or mortality. Although preliminary, these results are of potential major relevance, particularly in light of the exponential growth of the aging population, and the likely consequent increase in the number of hospitalisations. The clinical relevance of the findings reported here remains to be confirmed in future research.

Funding source

PLV is supported by a predoctoral contract granted by University of Alcalá (FPI2016). JSM is supported by a predoctoral contract granted by Spanish Ministry of Education, Culture and Sport (FPU14/03435). MI is supported by Spanish Ministry of Economy and Competitiveness and Fondos FEDER (PI17/01814). Research by AL is supported by Spanish Ministry of Economy and Competitiveness and Fondos FEDER (PI15/00558 and PI18/00139). Funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the article for publication.

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

Agmon, M., Zisberg, A., Gil, E., Rand, D., Gur-Yaish, N., Azriel, M., 2017. Association between 900 steps a day and functional decline in older hospitalized patients. JAMA Intern. Med. 177, 272–274. https://doi.org/10.1001/jamainternmed.2016.7266.

Bachmann, S., Finger, C., Huss, A., Egger, M., Stuck, A.E., Clough-Gorr, K.M., 2010. Inpatient rehabilitation specifically designed for geriatric patients: Systematic review and meta-analysis of randomised controlled trials. BMJ 340, 1230. https://doi.org/10.1136/bmj.c1718.

Bell, K.E., von Allmen, M.T., Devries, M.C., Phillips, S.M., 2016. Muscle Disuse as a Pivotal Problem in Sarcopenia-related Muscle Loss and Dysfunction. J Frailty Aging 5, 33–41. https://doi.org/10.14283/jfa.2016.78.

Biensø, R.S., Ringholm, S., Kiilerich, K., Aachmann-Andersen, N.J., Krogh-Madsen, R., Guerra, B., Plomgaard, P., Van Hall, G., Treebak, J.T., Saltin, B., Lundby, C., Calbet, J.A.L., Pilegaard, H., Wojtaszewski, J.F.P., 2012. GLUT4 and glycogen synthase are key players in bed rest-induced insulin resistance. Diabetes 61, 1090–1099. https://doi.org/10.2337/db11-0884.

Blanc-Bisson, C., Dechamps, A., Gouspillou, G., Dehail, P., Bourdel-Marchasson, I., 2008. A randomized controlled trial on early physiotherapy intervention versus usual care in acute car unit for elderly: Potential benefits in light of dietary intakes. J. Nutr. Heal. Aging 12, 395–399. https://doi.org/10.1007/BF02982673.

Boyd, C., Landefeld, C., Counsell, S., Palmer, R., Fortinsky, R., Kresevic, D., Burant, C., Covinsky, K., 2008. Recovery in Activities of Daily Living Among Older Adults Following Hospitalization for Acute Medical Illness. J. Am. Geriatr. Soc. 56, 2171–2179. https://doi.org/10.1111/j.1532-5415.2008.02023.x.Recovery.

Braun, T., Grüneberg, C., Süßmilch, K., Wiessmeier, M., Schwenk, I., Eggert, S., Machleit-Ebner, A., Harras, I., Thiel, C., 2019. An augmented prescribed exercise program (APEP) to improve mobility of older acute medical patients – a randomized, controlled pilot and feasibility trial. BMC Geriatr. 19, 1–20. https://doi.org/10.1186/s12877-019-1246-4.

Brown, C.J., Foley, K.T., Lowman, J.D., MacLennan, P.A., Razjouyan, J., Najafi, B., Locher, J., Allman, R.M., 2016. Comparison of posthospitalization function and community mobility in hospital mobility program and usual care patients a randomized clinical trial. JAMA Intern. Med. 176, 921–927. https://doi.org/10.1001/

jamainternmed.2016.1870.
Brown, C.J., Redden, D.T., Flood, K.L., Allman, R.M., 2009. The underrecognized epidemic of low mobility during hospitalization of older adults. J. Am. Geriatr. Soc. 57, 1660–1665. https://doi.org/10.1111/j.1532-5415.2009.02393.x.
Callen, B.L., Mahoney, J.E., Grieves, C.B., Wells, T.J., Enloe, M., 2004. Frequency of hallway ambulation by hospitalized older adults on medical units of an academic hospital. Geriatr. Nurs. (Minneap). 25, 212–217. https://doi.org/10.1016/j.gerinurse.2004.06.016.
Cohen, Y., Zisberg, A., Chayat, Y., Gur-Yaish, N., Gil, E., Levin, C., Rand, D., Agmon, M., 2019. Walking for Better Outcomes and Recovery: The Effect of WALK-FOR in Preventing Hospital-Associated Functional Decline Among Older Adults. Journals Gerontol. Ser. A Biol. Sci. Med. Sci. 74, 1664–1670.
Coker, R.H., Hays, N.P., Williams, R.H., Wolfe, R.R., Evans, W.J., 2015. Bed rest promotes reductions in walking speed, functional parameters, and aerobic fitness in older, healthy adults. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. 70, 91–96. https://doi.org/10.1093/gerona/glu123.
Corsonello, A., Lattanzio, F., Pedone, C., Garasto, S., Laino, I., Bustacchini, S., Pranno, L., Mazzei, B., Passarino, G., Incalzi, R.A., 2012. Prognostic significance of the short physical performance battery in older patients discharged from acute care hospitals. Rejuvenation Res. 15, 41–48. https://doi.org/10.1089/rej.2011.1215.
Covinsky, K.E., Pierluissi, E., Story, T.H.E.P.S., 2011. Hospitalization-Associated Disability "She Was Probably Able to Ambulate, but I'm Not Sure". JAMA 306, 1782–1793.
Dirks, M.L., Wall, B.T., Nilwik, R., Weerts, D.H.J.M., Verdijk, L.B., van Loon, L.J.C., 2014. Skeletal muscle disuse atrophy is not attenuated by dietary protein supplementation in healthy older men. J. Nutr. 144, 1196–1203. https://doi.org/10.3945/jn.114.194217.
Dirks, M.L., Wall, B.T., Van De Valk, B., Holloway, T.M., Holloway, G.P., Chabowski, A., Goossens, G.H., Van Loon, L.J., 2016. One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. Diabetes 65, 2862–2875. https://doi.org/10.2337/db15-1661.
Ehlenbach, W.J., Crane, P.K., Haneuse, S.J.P.A., Carson, S.S., Curtis, J.R., Larson, E.B., 2010. Association Between Acute Care and Critical Illness Hospitalization. JAMA 303, 763–770.
Fortinsky, R.H., Covinsky, K.E., Palmer, R.M., Landefeld, C.S., 1999. Effects of functional status changes before and during hospitalization on nursing home admission of older adults. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. 54, 521–526. https://doi.org/10.1093/gerona/54.10.M521.
Heldmann, P., Werner, C., Belala, N., Bauer, J.M., Hauer, K., 2019. Early inpatient rehabilitation for acutely hospitalized older patients: A systematic review of outcome measures. BMC Geriatr. 19, 1–24. https://doi.org/10.1186/s12877-019-1201-4.
Hu, F.W., Huang, Y.T., Lin, H.S., Chen, C.H., Chen, M.J., Chang, C.M., 2020. Effectiveness of a simplified reablement program to minimize functional decline in hospitalized older patients. Geriatr. Gerontol. Int. 1–7. https://doi.org/10.1111/ggi.13891.
Inouye, S.K., Peduzzi, P.N., Robison, J.T., Hughes, J.S., Horwitz, R.I., Concato, J., 1998. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 279, 1187–1198. https://doi.org/10.1001/jama.279.15.1187.
Jones, C.T., Lowe, A.J., MacGregor, L., Brand, C.A., Tweddle, N., Russell, D.M., 2006. A randomised controlled trial of an exercise intervention to reduce functional decline and health service utilisation in the hospitalised elderly. Australas. J. Ageing 25, 126–133. https://doi.org/10.1111/j.1741-6612.2006.00167.x.
Kanach, F.A., Pastva, A.M., Hall, K.S., Pavon, J.M., Morey, M.C., 2018. Effects of structured exercise interventions for older adults hospitalized with acute medical illness: A systematic review. J. Aging Phys. Act. 26, 284–303. https://doi.org/10.1123/japa.2016-0372.
Killey, B., Watt, E., 2006. The effect of extra walking on the mobility, independence and exercise self-efficacy of elderly hospital in-patients: a pilot study. Contemp. nurse a J. Aust. Nurs. Prof. 22, 120–133. https://doi.org/10.5172/conu.2006.22.1.120.
Kosse, N.M., Dutmer, A.L., Dasenbrock, L., Bauer, J.M., Lamoth, C.J.C., 2013. Effectiveness and feasibility of early physical rehabilitation programs for geriatric hospitalized patients: A systematic review. BMC Geriatr. 13. https://doi.org/10.1186/1471-2318-13-107.
Loyd, C., Markland, A.D., Zhang, Y., Fowler, M., Harper, S., Wright, N.C., Carter, C.S., Buford, T.W., Smith, C.H., Kennedy, R., Brown, C.J., 2019. Prevalence of Hospital-Associated Disability in Older Adults: A Meta-analysis. J. Am. Med. Dir. Assoc. In press. https://doi.org/10.1016/j.jamda.2019.09.015.
Mañas, A., Pozo-Cruz, B. del, Rodríguez-Gómez, I., Losa-Reyna, J., Rodríguez-Mañas, L., García-García, F.J., Ara, I., 2019. Can Physical Activity Offset the Detrimental Consequences of Sedentary Time on Frailty? A Moderation Analysis in 749 Older Adults Measured With Accelerometers. J. Am. Med. Dir. Assoc. https://doi.org/10.1016/j.jamda.2018.12.012. In press.
Martínez-Velilla, N., Cadore, E.L., Casas-Herrero, Idoate-Saralegui, F., Izquierdo, M., 2016. Physical activity and early rehabilitation in hospitalized elderly medical patients: Systematic review of randomized clinical trials. J. Nutr. Heal. Aging 20, 738–751. https://doi.org/10.1007/s12603-016-0683-4.
Martínez-Velilla, N., Casas-Herrero, N., Zambon-Ferraresi, F., López Sáez de Asteasu, M., Lucia, A., Galbete, A., García-Baztán, A., Alonso-Renedo, J., González-Glaría, B., Gonzalo-Lázaro, M., Aspezteguía-Iraizoz, I., Gutiérrez-Valencia, M., Rodríguez-Mañas, L., Izquierdo, M., 2019. Effect of Exercise Intervention on Functional Decline in Very Elderly Patients During Acute Hospitalization: A Randomized Clinical Trial. JAMA Intern. Med. 179, 28–36.
McCullagh, R., O'Connell, E., O'Meara, S., Dahly, D., O'Reilly, E., O'Connor, K., Horgan, N.F., Timmons, S., 2020. Augmented exercise in hospital improves physical performance and reduces negative post hospitalization events: A randomized controlled trial. BMC Geriatr. 20, 1–11. https://doi.org/10.1186/s12877-020-1436-0.
McGlory, C., von Allmen, M.T., Stokes, T., Morton, R.W., Hector, A.J., Lago, B.A., Raphenya, A.R., Smith, B.K., McArthur, A.G., Steinberg, G.R., Baker, S.K., Phillips, S.M., Newman, A., 2017. Failed Recovery of Glycemic Control and Myofibrillar Protein Synthesis With 2 wk of Physical Inactivity in Overweight, Prediabetic Older Adults. Journals Gerontol. Ser. A 00, 1–8. https://doi.org/10.1093/gerona/glx203.
McKelvie, S., Hall, A.M., Richmond, H.R., Finnegan, S., Lasserson, D., 2018. Improving the rehabilitation of older people after emergency hospital admission. Maturitas 111, 20–30. https://doi.org/10.1016/j.maturitas.2018.02.011.
Ortiz-Alonso, J., Bustamante-Ara, N., Valenzuela, P.L., Vidán, M., Rodríguez-Romo, G., Mayordomo-Cava, J., Javier-González, M., Hidalgo-gamarra, M., López-Tatis, M., Valades-Malagón, I., Santos-lozano, A., Lucia, A., Serra-Rexach, A., 2020. Effect of a simple exercise programme on hospitalisation-associated disability in older patients: a randomised controlled trial. JAMDA. https://doi.org/10.1101/19008151. In press.
Padula, C.A., Hughes, C., Baumhover, L., 2009. Impact of a nurse-driven mobility protocol on functional decline in hospitalized older adults. J. Nurs. Care Qual. 24, 325–331. https://doi.org/10.1097/NCQ.0b013e3181a4f79b.
Pavon, J.M., Sloane, R.J., Pieper, C.F., Colón-Emeric, C.S., Cohen, H.J., Gallagher, D., Hall, K.S., Morey, M.C., McCarty, M., Hastings, S.N., 2019. Accelerometer-Measured Hospital Physical Activity and Hospital-Acquired Disability in Older Adults. J. Am. Geriatr. Soc. In press. https://doi.org/10.1111/jgs.16231.
Rosenthal, R., 1991. Meta-analytic procedures for social research. Sage, Newbury Park, CA.
Sáez de Asteasu, Martinez-Velilla, N., Zambom-Ferraresi, F., Casas-Herrero, Á., Cadore, E.L., Galbete, A., Izquierdo, M., 2019a. Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: Secondary analysis of a randomized trial. PLOS Med. 16, e1002852. https://doi.org/10.1371/journal.pmed.1002852.
Sáez de Asteasu, Martinez-Velilla, N., Zambom-Ferraresi, F., Casas-Herrero, A., Lucia, A., Galbete, A., Izquierdo, M., 2019b. Physical Exercise Improves Function in Acutely Hospitalized Older Patients: Secondary Analysis of a Randomized Clinical Trial. J. Am. Med. Dir. Assoc. https://doi.org/10.1016/j.jamda.2019.04.001.
Sáez de Asteasu, Martínez-Velilla, N., Zambom-Ferraresi, F., Ramírez-Vélez, R., García-Hermoso, A., Cadore, E.L., Casas-Herrero, Á., Galbete, A., Izquierdo, M., 2020. Changes in muscle power after usual care or early structured exercise intervention in acutely hospitalized older adults. J. Cachexia. Sarcopenia Muscle. https://doi.org/10.1002/JCSM.12564.
Siebens, H., Aronow, H., Edwards, D., Ghasemi, Z., 2000. A randomized controlled trial of exercise to improve outcomes of acute hospitalization in older adults. J. Am. Geriatr. Soc. 48, 1545–1546.
Tanner, R.E., Brunker, L.B., Agergaard, J., Barrows, K.M., Briggs, R.A., Kwon, O.S., Young, L.M., Hopkins, P.N., Volpi, E., Marcus, R.L., Lastayo, P.C., Drummond, M.J., 2015. Age-related differences in lean mass, protein synthesis and skeletal muscle markers of proteolysis after bed rest and exercise rehabilitation. J. Physiol. 593, 4259–4273. https://doi.org/10.1113/JP270699.
Torres-Sánchez, I., Valenza, M.C., Cabrera-Martos, I., López-Torres, I., Benítez-Feliponi, Á., Conde-Valero, A., 2017. Effects of an Exercise Intervention in Frail Older Patients with Chronic Obstructive Pulmonary Disease Hospitalized due to an Exacerbation: A Randomized Controlled Trial. COPD J. Chronic Obstr. Pulm. Dis. 14, 37–42. https://doi.org/10.1080/15412555.2016.1209476.
Troosters, T., Probst, V.S., Crul, T., Pitta, F., Gayan-Ramirez, G., Decramer, M., Gosselink, R., 2010. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 181, 1072–1077. https://doi.org/10.1164/rccm.200908-1203OC.
Valenzuela, P., Castillo-García, A., Morales, J., Izquierdo, M., Serra-Rexach, J., Santos-Lozano, A., Lucia, A., 2019. Physical exercise in the oldest old. Compr. Physiol. 9, 1281–1304.
Valenzuela, P.L., Morales, J.S., Pareja-Galeano, H., Izquierdo, M., Emanuele, E., de la Villa, P., Lucia, A., 2018. Physical strategies to prevent disuse-induced functional decline in the elderly. Ageing Res. Rev. 47, 80–88. https://doi.org/10.1016/J.ARR.2018.07.003.
Valenzuela, P.L., Ortiz-alonso, J., Bustamante-ara, N., Vid, T., Hidalgo-gamarra, M., Myriel, L., Isabel, M., 2020. Individual Responsiveness to Physical Exercise Intervention in Acutely Hospitalized Older Adults. J. Clin. Med. 9, 797.
Verhagen, A., de Vet, H., de Bie, R., Kessels, A., Boers, M., Bouter, L., Knipschild, P., 1998. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J. Clin. Epidemiol. 51, 1235–1241.
Volpato, S., Cavalieri, M., Sioulis, F., Guerra, G., Maraldi, C., Zuliani, G., Fellin, R., Guralnik, J.M., 2011. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. 66 A, 89–96. https://doi.org/10.1093/gerona/glq167.
Wall, B.T., Snijders, T., Senden, J.M.G., Ottenbros, C.L.P., Gijsen, A.P., Verdijk, L.B., Van Loon, L.J.C., 2013. Disuse impairs the muscle protein synthetic response to protein ingestion in healthy men. J. Clin. Endocrinol. Metab. 98, 4872–4881. https://doi.org/10.1210/jc.2013-2098.
Wilson, R.S., Hebert, L.E., Scheer, P.A., Dong, X., Leurgens, S.E., Evans, D.A., 2012. Cognitive decline after hospitalization in a community population of older persons. Neurology 78, 950–956.
Zisberg, A., Shadmi, E., Sinoff, G., Gur-Yaish, N., Srulovici, E., Admi, H., 2011. Low mobility during hospitalization and functional decline in older adults. J. Am. Geriatr. Soc. 59, 266–273. https://doi.org/10.1111/j.1532-5415.2010.03276.x.

Effects of intradialytic exercise in patients receiving hemodialysis

In order to assess the effectiveness of an intradialytic exercise program for counteracting functional decline in patients with ESRD, we performed a clinical trial that was published in *Frontiers in Physiology* (impact factor 3.201, position 25/81, category: Physiology).[58] Our findings show that intradialytic exercise is overall effective for improving functional capacity and muscle strength, although a meaningful proportion of patients (>50%, particularly those with a better physical performance at baseline) did not benefit from the exercise program. A graphical abstract of this study is shown in Figure 7.

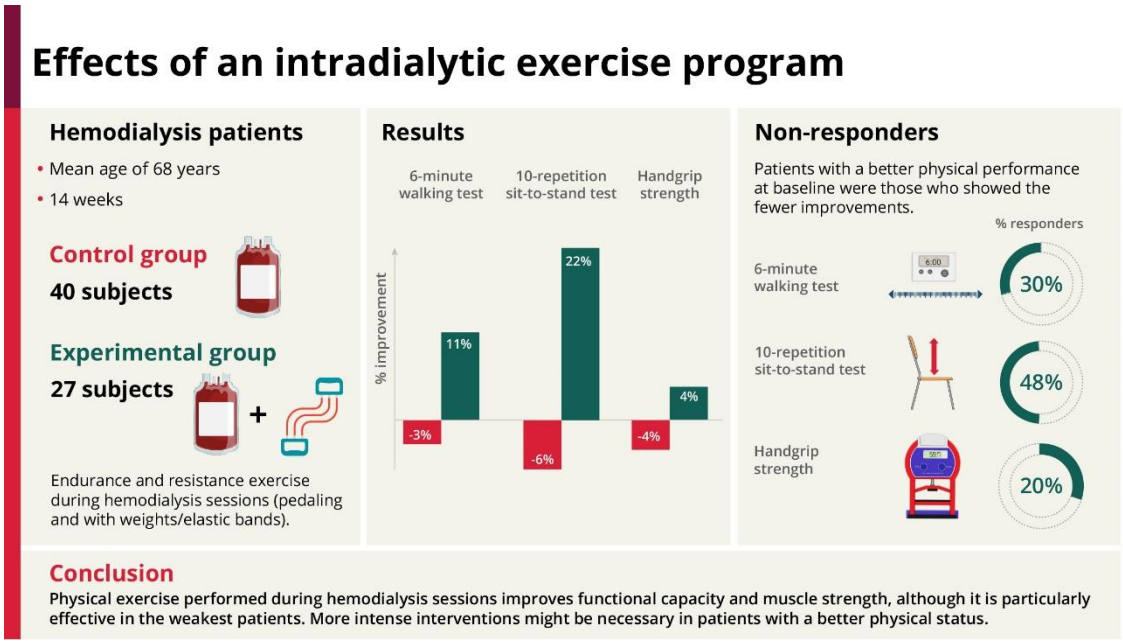


Figure 7. Summary of effects of an intradialytic exercise program in patients with end-stage renal disease.

frontiers in Physiology

ORIGINAL RESEARCH
published: 05 July 2018
doi: 10.3389/fphys.2018.00844

Intradialytic Exercise: One Size Doesn't Fit All

Pedro L. Valenzuela[1,2†], Ana de Alba[3†], Raquel Pedrero-Chamizo[4], Javier S. Morales[5], Fernando Cobo[3], Ana Botella[3], Marcela González-Gross[4], Margarita Pérez[5], Alejandro Lucia[5,6] and M. T. Marín-López[3]*

[1] Department of Systems Biology, Universidad de Alcalá, Madrid, Spain, [2] Department of Sport and Health, Spanish Agency for Health Protection in Sport (AEPSAD), Madrid, Spain, [3] Fundación Renal Íñigo Álvarez de Toledo, Madrid, Spain, [4] Faculty of Physical Activity and Sport Sciences, Technical University of Madrid, Madrid, Spain, [5] Faculty of Sport Sciences, European University of Madrid, Madrid, Spain, [6] Research Institute i+12 and CIBER de Envejecimiento y Fragilidad (CIBERFES), Madrid, Spain

OPEN ACCESS

Edited by:
Mikel Izquierdo, Universidad Pública de Navarra, Spain

Reviewed by:
Nir Eynon, Victoria University Melbourne, Australia
Steven John Fleck, University of Wisconsin–Eau Claire, United States

***Correspondence:**
Pedro L. Valenzuela
pedrol.valenzuela@edu.uah.es

[†] These authors have contributed equally to this work.

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *27 April 2018*
Accepted: *14 June 2018*
Published: *05 July 2018*

Citation:
Valenzuela PL, de Alba A, Pedrero-Chamizo R, Morales JS, Cobo F, Botella A, González-Gross M, Pérez M, Lucia A and Marín-López MT (2018) Intradialytic Exercise: One Size Doesn't Fit All. Front. Physiol. 9:844. doi: 10.3389/fphys.2018.00844

Purpose: Hemodialysis patients commonly have impaired physical performance and mental health. We studied the effects of an intradialytic exercise program on these variables.

Methods: 27 patients (33% women; 68 ± 13 years) were enrolled in a 14-week intradialytic endurance-resistance training program ('exercise' group, 40 programmed sessions per patient); 40 hemodialysis patients (28% women; 68 ± 11 years) performing no exercise during the same time length were used as controls. Endpoints included physical performance (6-min walk test [6MWT], 10-repetition sit to stand [STS-10] and handgrip strength), emotional status (Beck's depression inventory and State-Trait Anxiety Inventory), and mental and physical component scores of the short-from (SF)-12 Health Survey.

Results: There were no differences ($p > 0.05$) between groups at baseline for sex distribution, or mean age, body mass index and time spent on dialysis. Exercise benefits were observed for 6MWT (11 and −3% for the exercise and control groups, respectively; $p < 0.001$), STS-10 performance time (−22 and 6%; $p < 0.001$) and handgrip strength (4 and −4%; $p < 0.02$). No significant benefits ($p > 0.05$) were observed for emotional status endpoints or SF-12 component scores. Despite significant benefits on physical performance, the proportion of clinically meaningful responders was low (<50%). Responsiveness was dependent on baseline physical performance ($p < 0.05$) but not on age or sex ($p > 0.05$).

Conclusion: A 14-week intradialytic training program induced significant improvements on physical performance. However, the rate of clinically meaningful responders observed in the present study was low, being the level of responsiveness dependent on baseline physical status. Efforts to individualize exercise prescription are needed in clinical practice.

Keywords: hemodialysis, end-stage renal disease, chronic kidney disease, physical activity, training, mental health

INTRODUCTION

The prevalence of patients with end-stage renal disease is rapidly growing, especially among the elderly population and patients with comorbidities (particularly diabetes mellitus and hypertension) (Szczech and Lazar, 2004). Consequently, more than two million people are expected to be treated by dialysis for end-stage renal disease by 2030 (Szczech and Lazar, 2004).

Despite important progress in hemodialysis techniques and in the treatment of its associated comorbidities, patients have a much higher morbimortality risk than their healthy counterparts (Foley et al., 1998; Szczech and Lazar, 2004). Dialysis is associated with a deterioration of physical function and mental status. Muscle function (Leal et al., 2011b) and exercise capacity (Painter, 2005) are significantly lower in hemodialysis patients, presenting a peak oxygen consumption that is considerably lower (>50%) compared to their healthy sedentary peers (Painter, 2005). Emotional disorders such as anxiety and depression are prevalent among dialysis patients (Dziubek et al., 2016; King-Wing Ma and Kam-Tao Li, 2016), negatively affecting their social, financial and psychological well-being, as well as their quality of life (QoL) (Christensen and Ehlers, 2002).

Physical fitness is one of the strongest predictors of survival in dialysis patients, with low levels of physical activity and impaired physical performance being associated with increased mortality risk in this population (O'Hare et al., 2003; Sietsema et al., 2004; Stack et al., 2005; Roshanravan et al., 2013; Torino et al., 2014; Morishita et al., 2017). In addition, lower QoL and mental health are also strongly associated with higher risk of death and hospitalization (Knight et al., 2003; Mapes et al., 2003). Therefore, maintaining their physical and mental status closer to their healthy counterparts is of major importance.

Meta-analytical evidence supports the benefits of intradialytic exercise programs for the improvement of several health-related outcomes such as physical performance or mental health (Smart and Steele, 2011; Chung et al., 2017). Yet, exercise benefits in dialytic patients are typically reported under the assumption that the group average represents the response of most individuals. However, a wide interindividual variability can be observed in the human response to a similar training program, which results in subjects being classified as responders (those who achieve clinically meaningful benefits) or non-responders (those who experience a worsening or remain unchanged) (Mann et al., 2014). The aim of this study was to analyze the effects of a 14-week intradialytic combined exercise (endurance + resistance) training program on patients' mental and health status. In addition, we assessed the influence of baseline phenotype on the training response as well as individual variability in training responses to the study endpoints.

MATERIALS AND METHODS

Participants and Study Design

End-stage-renal disease patients undergoing hemodialysis were recruited for the study. Subjects were excluded if they presented one or more of the following conditions: myocardial infarction in the 6 weeks prior to the start of the exercise program, unstable angina, cerebrovascular disease or a high risk for recurrence, musculoskeletal or respiratory (e.g., chronic obstructive pulmonary disease) alterations, uncontrolled hypertension, peripheral vascular disease, active liver disease, osteoporosis, cardiac ejection fraction <45%, blood hemoglobin concentration <10 g/dL, or problematic vascular access (immature arteriovenous fistulas, high risk for extravasation). All participants had the procedures explained and provided written informed consent to participate in the study. The present study was approved by the institutional review board (P141115303, *Fundación Universitaria Hospital de Alcorcón*, Madrid, Spain).

The study took place between January 2015 and May 2016. Patients in the 'exercise' group had to participate in a 14-week intradialytic training program, whereas those of the 'control' group had to maintain their regular lifestyle during this time period without direct intervention from the personnel of this investigation. From a total of 235 patients undergoing hemodialysis in different dialysis centers, two cohorts of 86 and 74 patients met the inclusion criteria to participate as 'exercise' and 'control' group, respectively. From these, 12 and 31 patients, respectively, did not participate. Reasons not to participate were receiving a transplant, leaving the center, not signing the informed consent form after having the study explained to them, and not being interested. For the rest of patients, only those who performed at least two physical tests and two psychological tests at baseline were enrolled in the study. Finally, 27 and 40 patients were included in the exercise and control group, respectively. Participants' descriptive data are presented in **Table 1**.

Exercise Intervention

The intradialytic training intervention consisted of 14 weeks of combined endurance and resistance exercises. Training sessions were conducted at three different dialysis centers but were supervised by the same experienced fitness instructors. Training sessions were performed three times per week and lasted approximately 60 min. A total of 40 training sessions were planned per subject during the intervention portion of the study.

Training sessions started with a warm-up consisting of respiratory and joint mobility exercises. During the main part of the sessions, both resistance and endurance exercises were performed. Resistance exercises included ankle plantarflexion and dorsiflexion, combined knee and hip flexion and extension, hip abduction and adduction, and abdominal exercises. These

TABLE 1 | Descriptive baseline characteristics of the participants.

	Control	Exercise	*p*-value
Women (%)	28	33	0.79
Age (years)	68 ± 11	68 ± 13	0.92
BMI ($kg \cdot m^{-2}$)	27 ± 5	27 ± 6	0.99
Dialysis prescription ($hours \cdot week^{-1}$)	11 ± 1	11 ± 1	0.51
Time on dialysis (years)	5 ± 4	7 ± 5	0.08

Data are Mean ± SD. Abbreviations: BMI, body mass index.

exercises were performed using elastic bands, Styrofoam balls and ankle weights. Endurance exercise consisted of pedaling on a mini bike for 30 min at an intensity corresponding to 12–14 points in the Borg's 6–20 scale (Borg, 1998).

Endpoints

Endpoints were assessed the week before (baseline) and after (post-intervention) the 14-week intervention. Assessment was done on dialysis days, with each participant being tested at the same time of the day (i.e., always in the morning or in the afternoon, before starting dialysis). Before the testing sessions, participants were individually instructed on how to perform all tests with detailed explanations and visual examples. Two testing sessions per patient were required to perform all the tests at each time point, one for all physical performance tests and another one for psychological evaluation. The tests were always performed in the same order.

Physical Performance

We assessed patients' performance in the 10-repetition sit to stand (STS-10), handgrip strength and 6-min walk (6MWT) tests (performed in this order), which are some of the most popular fitness tests in dialysis patients (Koufaki and Kouidi, 2010) and present an excellent test-retest reliability in this population (Segura-Ortí and Martínez-Olmos, 2011).

The STS-10, an index of lower-extremity strength (Csuka and McCarty, 1985), measures the time (in seconds) required to perform 10 consecutive repetitions of sitting down and getting up from a chair. Participants began the test with their arms crossed on their chest and sitting with their back against the chair. They were instructed to perform the task "as fast as possible," starting and finishing at the sitting position. Time was measured with a stopwatch (ONstart 100, Geonaute, France) to the nearest 0.1 s. This test has previously demonstrated a good test-retest reliability in hemodialysis patients (intra-class correlation coefficient [ICC] = 0.88) (Segura-Ortí and Martínez-Olmos, 2011).

Maximal isometric handgrip force has been suggested as a useful tool for the continuous assessment of muscle mass and function in dialysis patients (Leal et al., 2011a). It was measured in both hands using a manual dynamometer (T.K.K.5401, Takei Scientific Instruments, Japan) while participants were in a standing position, with the arm extended and parallel to the body, and without moving the wrist. They performed two maximal repetitions with each hand interspersed with 1-min rest periods between trials, and the mean of all four trials (combined handgrip strength) was analyzed. This test has also proven highly reliable in hemodialysis patients (ICC = 0.95 and 0.96 for the dominant and non-dominant hand, respectively) (Segura-Ortí and Martínez-Olmos, 2011).

The 6MWT was used as a marker of endurance capacity (Rikli and Jones, 1998). It was performed on a 17-meter corridor with marks on every meter, and time was measured with a chronometer (ONstart 100, Geonaute, France). Participants were asked to cover the greatest distance possible during 6 min by walking (not running) continuously and turning around at the final mark. No verbal encouragement was given during the test; however, feedback regarding the remaining time was available. Participants were allowed to rest during the test, and to use any ambulation aid (e.g., crutches) that they used during daily life. A very high test-retest reliability has been previously reported for this test in hemodialysis patients (ICC = 0.94) (Segura-Ortí and Martínez-Olmos, 2011).

Mental and Health Status

Changes in depression symptoms were assessed using the Beck Depression Inventory (BDI) (Beck et al., 1996). In this self-reported questionnaire 21 items are rated on a four-point severity scale and summed to give a total score, with a higher score being suggestive of more severe depression. The BDI has proven a valid depression screening tool in dialysis patients (Preljevic et al., 2012), being one of the most commonly used questionnaires to assess this condition in this patient population (King-Wing Ma and Kam-Tao Li, 2016). This questionnaire has previously yielded high values of internal consistency (Cronbach's $\alpha = 0.89$), sensitivity (0.82) and specificity (0.87–0.89) in dialysis patients (Preljevic et al., 2012). Test–retest coefficients in other populations have been reported to range from 0.62 (7-week interval) to 0.93 (1-week interval) (Julian, 2011).

Health-related QoL (HRQoL) was assessed using the Short-Form 12 (SF-12) health survey, a short version of the SF-36 (Ware and Sherbourne, 1992). A physical (PCS) and a mental component score (MCS) are calculated from this self-reported questionnaire. SF-12 has previously proven reliable in a 6-month longitudinal study performed with dialysis patients (ICC = 0.90 and 0.86 for MCS and PCS, respectively) (Loosman et al., 2015). Moreover, SF-12 scores are associated with short-term and long-term mortality in this population (Loosman et al., 2015).

The level of anxiety was assessed using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970). We specifically analyzed the anxiety subscale. This test has previously shown a good internal consistency (Cronbach's $\alpha = 0.86$–0.95) and reliability over time ($r = 0.65$–0.75) (Spielberger et al., 1970; Julian, 2011).

Statistical Analysis

All the participants assessed at baseline were considered to be part of the study. Missing individual data at post-intervention were imputed with the 'baseline-observation-carried forward' method, that is, baseline values were used when these data were missing. The normal distribution (Shapiro-Wilk test) and homoscedasticity (Levene's test) of the data were checked before any statistical treatment. Non-normally distributed data (results from STAI and BDI) were log-transformed prior to its analysis. Differences in proportions were evaluated using Pearson's chi-squared test. Differences in baseline characteristics were analyzed using unpaired Student's *t*-tests. Endpoints were analyzed by a two-way mixed ANOVA with time points (baseline and post-intervention) as the within-subject factor and intervention groups (control or exercise) as the between-subject factor. The effect size (partial eta-squared, η_p^2) of the significant group x time interactions was calculated and considered small (>0.01) moderate (>0.06) or large (>0.14) (Cohen, 1988). *Post hoc*

analysis (Bonferroni test) was conducted when a significant interaction (group × time) effect was found.

The rate of clinically meaningful responders was calculated in those endpoints in which a beneficial effect of exercise (i.e., significant group x time interaction) was found. Responsiveness was defined as beneficial changes that exceeded two times the standard error of measurement (SEM) (Hopkins, 2000). The responsiveness threshold for the physical tests was set at 3 kg, 7.2 s, and 56.8 m for handgrip strength, STS-10 and 6MWT, respectively, attending to the SEM values previously reported for these tests in dialysis patients (Segura-Ortí and Martínez-Olmos, 2011). The magnitude of the differences (effect size, ES) in baseline values between responders and non-responders was determined through standardized mean differences (Hedges' g). Pearson's correlation analyses (for physical performance and age) and Pearson's chi-square test (for sex) were used to determine the influence of baseline phenotype on training responsiveness. All analyses were performed using a statistical Package (SPSS, version 23.0).

RESULTS

There were no significant differences between control and exercise groups in baseline characteristics (**Table 1**). All subjects in the exercise group completed at least 80% of the planned training sessions. No major adverse events or health-related issues attributable to exercise were noted.

Four subjects in each group could not complete the baseline 10-STS assessment due to excessive weakness or mobility limitations (i.e., use of crutches), and therefore the sample analyzed for this test was of 36 and 23 for the control and the exercise group, respectively. After the 14-week intervention four subjects in the control group could not perform the 10-STS and one subject in this same group could not perform the psychological tests, and thus we used their baseline values.

No significant changes in physical performance measures were observed in the control group between baseline and post-intervention. By contrast, a significant improvement was observed in the exercise group for 6MWT ($p = 0.006$, ES = 0.31), STS-10 ($p < 0.001$, ES = 0.59) and combined handgrip strength ($p = 0.027$, ES = 0.12). Significant interactions (group × time) with moderate to large effect sizes were found for all physical performance measures (**Table 2**). *Post hoc* analyses revealed significant differences between groups at post-intervention for 6MWT ($p = 0.005$), STS-10 ($p < 0.001$) and combined handgrip strength ($p = 0.017$).

Despite statistically significant benefits, only 30, 46, and 20% of subjects in the exercise group were clinically meaningful responders for 6MWT, STS-10 and handgrip strength test, respectively. Of note, responsiveness was dependent on baseline physical fitness, that is, participants with lower baseline physical fitness showed greater improvements. Indeed, significant differences were found between responders and non-responders for baseline physical performance (**Figure 1**), and a significant inverse relationship was observed between baseline combined handgrip strength and 6MWT, on one hand, and the relative performance improvement in these tests, on the other (**Figure 2**). There were no significant differences between sexes for the rate of responders observed in 6MWT (33 and 22% for men and women, respectively; $p = 0.882$), STS-10 (53 and 33%, respectively; $p = 0.597$) or handgrip strength test (11 and 44%, respectively; $p = 0.141$). No significant relationship ($p > 0.05$) was observed between age and relative improvement on physical performance for any test.

Regarding mental status, BDI scores significantly decreased in the exercise group at post-intervention compared to baseline ($p = 0.006$, ES = 0.29), whereas no significant changes were

TABLE 2 | Effects of an intradialytic exercise program on markers of physical and mental health.

End point	Group	n with baseline data	Baseline	Post-intervention	Change (95% CI)	Group × Time effect	Effect size (η_p^2)[a]
6MWT (m)	Control	40	341 ± 127	330 ± 118	−11 (−27, 5)	**0.001**	0.160
	Exercise	27	380 ± 131	422 ± 136	42 (13, 70)		
STS-10 (s)	Control	36	32 ± 11	34 ± 12	2 (−1, 5)	**<0.001**	0.203
	Exercise	23	26 ± 10	21 ± 8	−6 (−8, −4)		
Handgrip (kg)	Control	40	25 ± 8	24 ± 8	−1 (−2, 0)	**0.02**	0.084
	Exercise	27	28 ± 8	29 ± 8	1 (0, 2)		
STAI-S	Control	40	18 ± 13	18 ± 12	0 (−2, 2)	0.10	–
	Exercise	27	19 ± 9	17 ± 10	−2 (−5, 2)		
BDI	Control	40	15 ± 13	14 ± 10	−1 (−3, 2)	0.32	–
	Exercise	27	10 ± 8	8 ± 7	−2 (−4, −1)		
PCS	Control	40	61 ± 17	66 ± 16	5 (0, 10)	0.36	-
	Exercise	27	62 ± 20	63 ± 23	1 (−5, 8)		
MCS	Control	40	70 ± 20	73 ± 16	3 (−1, 8)	0.54	–
	Exercise	27	75 ± 14	76 ± 15	1 (−3, 5)		

Data are mean ± SD. Significant p-values are highlighted in bold. Handgrip strength corresponds to the mean of the two arms. Abbreviations: 6MWT, six minute-walk test; 95% CI, 95% confidence intervals; BDI, Beck's depression inventory; MCS, mental component summary; PCS, physical component summary; STAI-S, State-Trait Anxiety Inventory; STS-10, sit to stand test. 4 and 1 subjects of the control group could not perform the STS-10 and the psychological tests, respectively, at post-intervention, and their baseline values were used. Data from STAI-S and BDI were log-transformed prior to its analysis, but are shown as raw data for the sake of clarity.

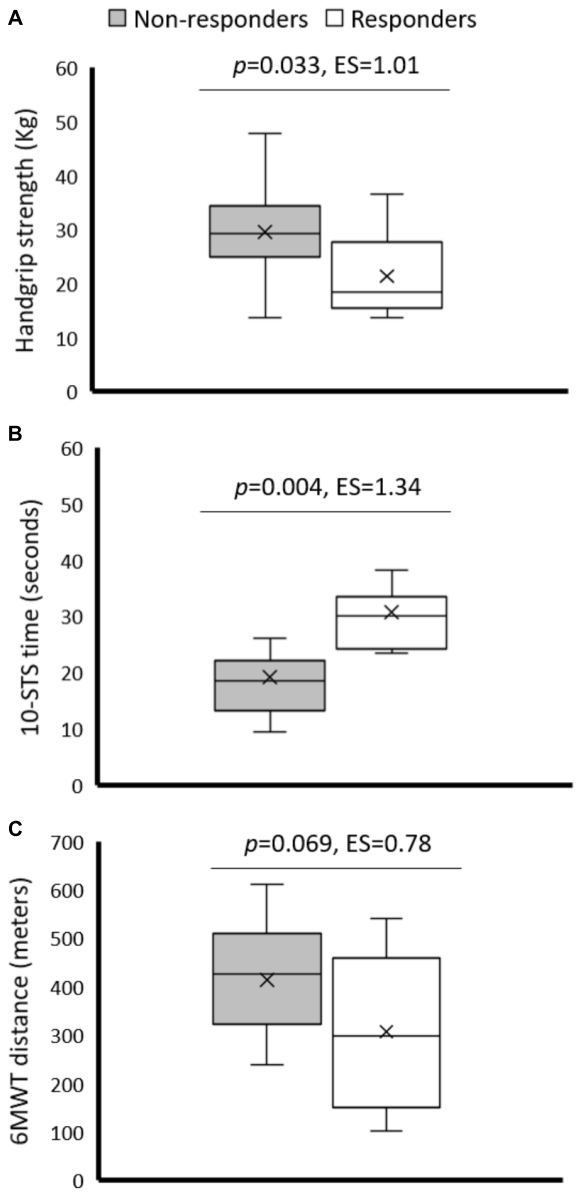


FIGURE 1 | Differences in baseline performance for combined handgrip strength **(A)** 10-repetition sit to stand **(B)** and 6-min walk test **(C)** between responders and non-responders to the intradialytic training program.

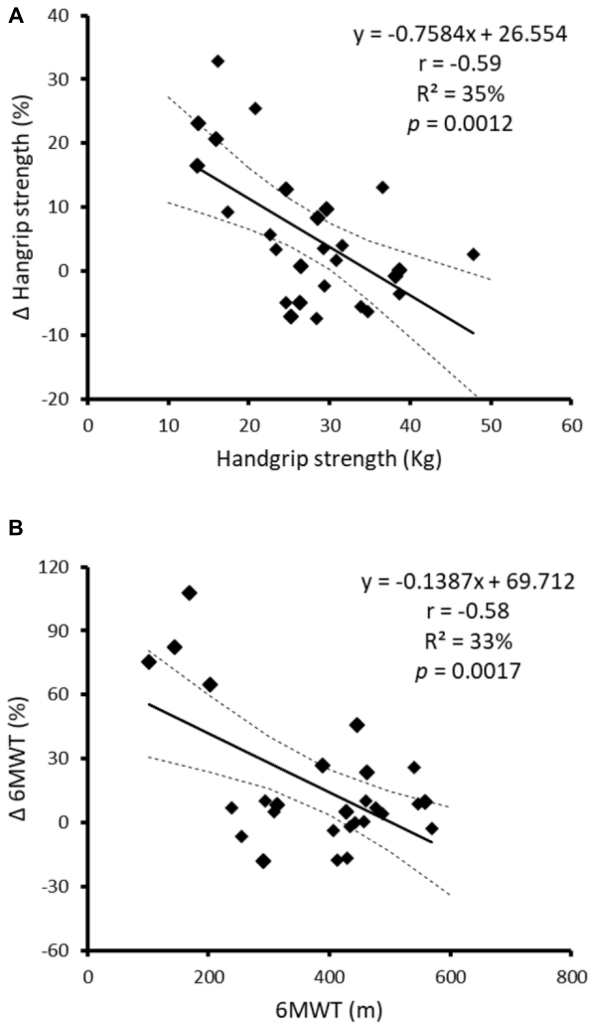


FIGURE 2 | Relationship between baseline performance for combined handgrip strength **(A)** and 6-min walk distance **(B)** with the change observed in these tests after the intradialytic training program. Solid and dashed lines represent regression line and 90% confidence intervals, respectively.

observed in the control group (**Table 2**). No significant differences ($p > 0.05$) between baseline and post-intervention were observed for any of the other mental and health status endpoints in the control or exercise group (**Table 2**). No significant interaction (group x time) was found for any of the mental and health status endpoints (**Table 2**).

DISCUSSION

The present results show that a 14-week intradialytic training program including endurance and resistance exercise induced improvements in mean values of physical performance, which are significantly lower in this population than in their healthy counterparts (Painter, 2005; Leal et al., 2011b). Specifically, significant improvements were observed for the average value of 6MWT, a valid predictor of mortality, cardiovascular events and hospitalization in dialysis patients (Torino et al., 2014). Exercise training also resulted in an increased strength of the lower limb muscles (as reflected by a lower time on average to complete the STS-10 test), which is important because an impaired physical performance of the lower extremities is strongly associated with all-cause mortality in these patients (Roshanravan et al., 2013). We also found an exercise-training induced improvement in handgrip strength, with decreases in this variable being related to a decreased inflammatory status and higher muscle mass and survival expectancy in this population (Leal et al., 2011a). Therefore, these results are of major clinical importance,

as they suggest that an intradialytic exercise program can attenuate dialysis-associated physical impairment and thus might also potentially reduce morbimortality risk in these patients (Morishita et al., 2017).

The effectiveness of intradialytic training programs for the improvement of physical performance has been previously demonstrated (Smart and Steele, 2011; Chung et al., 2017). Although the response to exercise interventions is commonly described in general terms under the assumption that the group average represents the response of most individuals (Mann et al., 2014), it has now been demonstrated that a considerable individual variability can be observed even in tightly controlled studies (Yan et al., 2017). In this context, an interesting finding of the present study is that, despite significant improvements in mean physical performance, the rate of clinically meaningful responders was overall low (<50%). Several hypotheses have been proposed to account for individual variability in response to exercise training (Mann et al., 2014). In our study, baseline physical performance - but not participants' age or sex - partly conditioned the level of responsiveness to the training program, with the less fit patients at baseline being those showing greater benefits. These results suggest that the training stimulus was high enough to induce clinically meaningful improvements in less fit subjects but not in their fitter peers. Notwithstanding, even non-responders presented a lower physical performance at baseline than expected for their age (Casanova et al., 2011; Massy-Westropp et al., 2011). Therefore, efforts to enhance responsiveness in these subjects are needed, which might probably involve applying a higher training stimulus (e.g., higher intensity or volume) (Mann et al., 2014).

Although in agreement with our results some studies have found no changes in variables such as HRQoL or depression after intradialytic training programs (van Vilsteren et al., 2005; Parsons et al., 2006), most studies have reported benefits on these psychological variables (Suh et al., 2002; Levendoğlu et al., 2004; Ouzouni et al., 2009; Dziubek et al., 2016; Frih et al., 2017). Interestingly, the level of anxiety observed in our patients was overall low, with only 4% of subjects in the intervention group presenting a STAI score higher than 40, which is the proposed cut-off for detecting clinically significant symptoms of anxiety) (Knight et al., 1983; Julian, 2011). HRQoL was also surprisingly good, with the observed mean MCS and PCS being higher than those previously reported in other dialysis populations (Mapes et al., 2003; Lacson et al., 2010; Frih et al., 2017). The lack of significant differences in these variables in our study might have been due to the low prevalence of psychological disorders in the analyzed sample, which can be a result of the psychological therapy that all subjects received since they started dialysis. Nevertheless, a significant reduction of 23% in mean BDI scores was observed after the exercise program in the present study, and a reduction of >17.5% has proven to be the threshold above which depressive individuals report feeling better (Button et al., 2015). Therefore, the observed benefits of exercise on depression levels could be of clinical importance despite no statistically significant differences between groups.

Considering the importance of physical activity and performance for dialysis patients (O'Hare et al., 2003; Sietsema et al., 2004; Stack et al., 2005; Matsuzawa et al., 2012; Roshanravan et al., 2013) and their low levels of physical activity (Johansen et al., 2010), promoting physical activity in this population should be a priority. Intradialytic exercise programs have proven safe and effective not only for improving physical performance (Smart and Steele, 2011; Chung et al., 2017) but also dialysis efficacy (Parsons et al., 2006), and therefore these programs should be routinely included in clinical practice. Nevertheless, the present study highlights the need of individualizing training programs so as to achieve an optimal stimulus for every patient.

Our study has some limitations, including mainly the lack of subjects' familiarization sessions with the tests and the fact that we did not perform a randomized controlled trial. In addition, several potential confounders which were not considered here have been proposed to influence inter-individual variability in response to a training stimulus. Particularly a commonly overlooked source of error is within-subject variability, with recent research providing some insights into its importance (Hecksteden et al., 2015, 2018; Lindholm et al., 2016) and another ongoing project, the Gene Smart study, currently embracing this concept (Yan et al., 2017). However, applying the designs that allow to control for confounders like within-subject variability (e.g., performing repeated tests both before and after the intervention, or using a crossover study with repeated training intervention) might not be feasible in patient populations such as the present one. While keeping the aforementioned limitations in mind, a major strength and novelty of our approach was the individualized analysis of training responses, which allowed us to estimate the rate of clinically meaningful responders.

CONCLUSION

A 14-week intradialytic endurance-resistance training program improved patients' physical performance on average. Yet, baseline physical status affected the level of responsiveness to the training program, with only those patients presenting the lowest physical fitness at the beginning of the intervention obtaining clinically meaningful benefits from the training program. Efforts to individualize exercise prescription are needed in clinical practice to enhance responsiveness. Future reach might determine if applying a higher training stimulus (i.e., higher intensity or volume) in the fitter subjects actually results in a clinically meaningful response.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the institutional review board of Fundación Universitaria Hospital de Alcorcón (Madrid, Spain). The protocol was approved by the institutional review board of Fundación Universitaria Hospital de Alcorcón (Madrid, Spain). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

AB, RP-C, MG-G, and MP conceived, designed, and supervised the study. AdA, FC, and MM-L supervised the training sessions and performed the evaluations. PV and JM analyzed the data. PV drafted the manuscript. All authors significantly contributed to the final version of the manuscript.

FUNDING

PV is supported by a predoctoral contract granted by the University of Alcalá (FPI2016). JM is supported by a predoctoral contract granted by Ministry of Education, Culture and Sport (FPU14/03435). AL is supported by grants from Spanish Ministry of Economy and Competitiveness and Fondos FEDER [Fondo de Investigaciones Sanitarias (FIS), grant no. PI15/00558].

ACKNOWLEDGMENTS

We gratefully thank all participants, Fundación Renal Íñigo Álvarez de Toledo, and especially its general director, Blanca Miranda, for their support. We also thank Fundación Real Madrid for their technical help with the training sessions.

REFERENCES

Beck, A., Steer, R. A., and Brown, G. K. (1996). *Beck Depression Inventory*, 2nd Edn. San Antonio, TX: The Psycological Corporation.

Borg, G. (1998). *Borg's Perceived Exertion and Pain Scales*, 7th Edn. Champaign, IL: Human Kinetics.

Button, K. S., Kounali, D., Thomas, L., Wiles, N. J., Peters, T. J., Welton, N. J., et al. (2015). Minimal clinically important difference on the Beck Depression Inventory-II according to the patient's perspective. *Psychol. Med.* 45, 3269–3279. doi: 10.1017/S0033291715001270

Casanova, C., Celli, B. R., Barria, P., Casas, A., Cote, C., De Torres, J. P., et al. (2011). The 6-min walk distance in healthy subjects: reference standards from seven countries. *Eur. Respir. J.* 37, 150–156. doi: 10.1183/09031936.00194909

Christensen, A. J., and Ehlers, S. L. (2002). Psychological factors in end-stage renal disease: an emerging context for behavioral medicine research. *J. Consult. Clin. Psychol.* 70, 712–724. doi: 10.1037//0022-006X.70.3.712

Chung, Y. C., Yeh, M. L., and Liu, Y. M. (2017). Effects of intradialytic exercise on the physical function, depression and quality of life for haemodialysis patients: a systematic review and meta-analysis of randomised controlled trials. *J. Clin. Nurs.* 26, 1801–1813. doi: 10.1111/jocn.13514

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*, 2nd Edn. Hillsdale, NJ: Lawrence Erlbaum Associates. doi: 10.1234/12345678

Csuka, M., and McCarty, D. J. (1985). Simple method for measurement of lower extremity muscle strength. *Am. J. Med.* 78, 77–81. doi: 10.1016/0002-9343(85)90465-6

Dziubek, W., Kowalska, J., Kusztal, M., Rogowski, Ł., Gołębiowski, T., Nikifur, M., et al. (2016). The level of anxiety and depression in dialysis patients undertaking regular physical exercise training - a preliminary study. *Kidney Blood Press. Res.* 41, 86–98. doi: 10.1159/000368548

Foley, R., Parfrey, P., and Sarnak, M. (1998). Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am. J. Kidney Dis.* 32, S112–S119. doi: 10.1053/ajkd.1998.v32.pm9820470

Frih, B., Jaafar, H., Mkacher, W., Ben Salah, Z., Hammami, M., and Frih, A. (2017). The effect of interdialytic combined resistance and aerobic exercise training on health related outcomes in chronic hemodialysis patients: the Tunisian randomized controlled study. *Front. Physiol.* 8:288. doi: 10.3389/fphys.2017.00288

Hecksteden, A., Kraushaar, J., Scharhag-Rosenberger, F., Theisen, D., Senn, S., and Meyer, T. (2015). Individual response to exercise training – a statistical perspective. *J. Appl. Physiol.* 118, 1450–1459. doi: 10.1152/japplphysiol.00714.2014

Hecksteden, A., Pitsch, W., Rosenberger, F., and Meyer, T. (2018). Repeated testing for the assessment of individual response to exercise training. *J. Appl. Physiol.* doi: 10.1152/japplphysiol.00896.2017 [Epub ahead of print].

Hopkins, W. G. (2000). Measures of reliability in sports medicine and science. *Sports Med.* 30, 1–15. doi: 10.2165/00007256-200030010-00001

Johansen, K. L., Chertow, G. M., Kutner, N. G., Dalrymple, L. S., Grimes, B. A., and Kaysen, G. A. (2010). Low level of self-reported physical activity in ambulatory patients new to dialysis. *Kidney Int.* 78, 1164–1170. doi: 10.1038/ki.2010.312

Julian, L. J. (2011). Measures of Anxiety. *Arthritis Care* 63, 0–11. doi: 10.1002/acr.20561

King-Wing Ma, T., and Kam-Tao Li, P. (2016). Depression in dialysis patients. *Nephrology (Carlton)* 21, 639–646. doi: 10.1111/nep.12742

Knight, E. L., Ofsthun, N., Teng, M., Lazarus, J. M., and Curhan, G. C. (2003). The association between mental health, physical function, and hemodialysis mortality. *Kidney Int.* 63, 1843–1851. doi: 10.1046/j.1523-1755.2003.00931.x

Knight, R. G., Waal Manning, H. J., and Spears, G. F. (1983). Some norms and reliability data for the State–Trait Anxiety Inventory and the Zung Self-Rating Depression scale. *Br. J. Clin. Psychol.* 22, 245–249. doi: 10.1111/j.2044-8260.1983.tb00610.x

Koufaki, P., and Kouidi, E. (2010). Current best evidence recommendations on measurement and interpretation of physical function in patients with chronic kidney disease. *Sports Med.* 40, 1055–1074. doi: 10.2165/11536880-000000000-00000

Lacson, E., Xu, J., Lin, S. F., Dean, S. G., Lazarus, J. M., and Hakim, R. M. (2010). A comparison of SF-36 and SF-12 composite scores and subsequent hospitalization and mortality risks in long-term dialysis patients. *Clin. J. Am. Soc. Nephrol.* 5, 252–260. doi: 10.2215/CJN.07231009

Leal, V. O., Mafra, D., Fouque, D., and Anjos, L. A. (2011a). Use of handgrip strength in the assessment of the muscle function of chronic kidney disease patients on dialysis: a systematic review. *Nephrol. Dial. Transplant.* 26, 1354–1360. doi: 10.1093/ndt/gfq487

Leal, V. O., Stockler-Pinto, M. B., Farage, N. E., Aranha, L. N., Fouque, D., Anjos, L. A., et al. (2011b). Handgrip strength and its dialysis determinants in hemodialysis patients. *Nutrition* 27, 1125–1129. doi: 10.1016/j.nut.2010.12.012

Levendoğlu, F., Altintepe, L. L., Okudan, N., Uğurlu, H., Gökbel, H., Tonbul, Z., et al. (2004). A twelve week exercise program improves the psychological status, quality of life and work capacity in hemodialysis patients. *J. Nephrol.* 17, 826–832.

Lindholm, M. E., Giacomello, S., Werne Solnestam, B., Fischer, H., Huss, M., Kjellqvist, S., et al. (2016). The impact of endurance training on human skeletal muscle memory, global isoform expression and novel transcripts. *PLoS Genet.* 12:e1006294. doi: 10.1371/journal.pgen.1006294

Loosman, W. L., Hoekstra, T., Van Dijk, S., Terwee, C. B., Honig, A., Siegert, C. E. H., et al. (2015). Short-Form 12 or Short-Form 36 to measure quality-of-life changes in dialysis patients? *Nephrol. Dial. Transplant.* 30, 1170–1176. doi: 10.1093/ndt/gfv066

Mann, T. N., Lamberts, R. P., and Lambert, M. I. (2014). High responders and low responders: factors associated with individual variation in response to standardized training. *Sports Med.* 44, 1113–1124. doi: 10.1007/s40279-014-0197-3

Mapes, D. L., Lopes, A. A., Satayathum, S., McCullough, K. P., Goodkin, D. A., Locatelli, F., et al. (2003). Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int.* 64, 339–349. doi: 10.1046/j.1523-1755.2003.00072.x

Massy-Westropp, N. M., Gill, T. K., Taylor, A. W., Bohannon, R. W., and Hill, C. L. (2011). Hand Grip Strength: age and gender stratified normative data in a population-based study. *BMC Res. Notes* 4:127. doi: 10.1186/1756-0500-4-127

Matsuzawa, R., Matsunaga, A., Wang, G., Kutsuna, T., Ishii, A., Abe, Y., et al. (2012). Habitual physical activity measured by accelerometer and survival in

maintenance hemodialysis patients. *Clin. J. Am. Soc. Nephrol.* 7, 2010–2016. doi: 10.2215/CJN.03660412

Morishita, S., Tsubaki, A., and Shirai, N. (2017). Physical function was related to mortality in patients with chronic kidney disease and dialysis. *Hemodial. Int.* 21, 483–489. doi: 10.1111/hdi.12564

O'Hare, A. M., Tawney, K., Bacchetti, P., and Johansen, K. L. (2003). Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2. *Am. J. Kidney Dis.* 41, 447–454. doi: 10.1053/ajkd.2003.50055

Ouzouni, S., Kouidi, E., Sioulis, A., Grekas, D., and Deligiannis, A. (2009). Effects of intradialytic exercise training on health-related quality of life indices in haemodialysis patients. *Clin. Rehabil.* 23, 53–60. doi: 10.1177/0269215508096760

Painter, P. (2005). Physical functioning in end-stage renal disease patients: update 2005. *Hemodial. Int.* 9, 218–235. doi: 10.1111/j.1492-7535.2005.01136.x

Parsons, T. L., Toffelmire, E. B., and King-VanVlack, C. E. (2006). Exercise training during hemodialysis improves dialysis efficacy and physical performance. *Arch. Phys. Med. Rehabil.* 87, 680–687. doi: 10.1016/j.apmr.2005.12.044

Preljevic, V. T., Østhus, T. B. H., Sandvik, L., Opjordsmoen, S., Nordhus, I. H., Os, I., et al. (2012). Screening for anxiety and depression in dialysis patients: comparison of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory. *J. Psychosom. Res.* 73, 139–144. doi: 10.1016/j.jpsychores.2012.04.015

Rikli, R. E., and Jones, C. J. (1998). The reliability and validity of a 6-minute walk test as a measure of physical endurance in older adults. *J. Aging Phys. Act.* 6, 363–375. doi: 10.1097/00005768-199805001-199805421

Roshanravan, B., Robinson-Cohen, C., Patel, K. V., Ayers, E., Littman, A. J., de Boer, I. H., et al. (2013). Association between physical performance and all-cause mortality in CKD. *J. Am. Soc. Nephrol.* 24, 822–830. doi: 10.1681/ASN.2012070702

Segura-Ortí, E., and Martínez-Olmos, F. J. (2011). Test-retest reliability and minimal detectable change scores for sit-to-stand-to-sit tests, the six-minute walk test, the one-leg heel-rise test, and handgrip strength in people undergoing hemodialysis. *Phys. Ther.* 91, 1244–1252. doi: 10.2522/ptj.20100141

Sietsema, K. E., Amato, A., Adler, S. G., and Brass, E. P. (2004). Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int.* 65, 719–724. doi: 10.1111/j.1523-1755.2004.00411.x

Smart, N., and Steele, M. (2011). Exercise training in haemodialysis patients: a systematic review and meta-analysis. *Nephrology (Carlton)* 16, 626–632. doi: 10.1111/j.1440-1797.2011.01471.x

Spielberger C. D., Gorsuch, R., and Lushene, R. (1970). *Test Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Stack, A. G., Molony, D. A., Rives, T., Tyson, J., and Murthy, B. V. R. (2005). Association of physical activity with mortality in the US dialysis population. *Am. J. Kidney Dis.* 45, 690–701. doi: 10.1053/j.ajkd.2004.12.013

Suh, M. R., Jung, H., Kim, S., Park, J., and Yang, W. (2002). Effects of regular exercise on anxiety, depression, and quality of life in maintenance hemodialysis patients. *Ren. Fail.* 24, 337–345. doi: 10.1081/JDI-120005367

Szczech, L. A., and Lazar, I. L. (2004). Projecting the United States ESRD population: issues regarding treatment of patients with ESRD. *Kidney Int.* 66(Suppl. 90), S3–S7. doi: 10.1111/j.1523-1755.2004.09002.x

Torino, C., Manfredini, F., Bolignano, D., Aucella, F., Baggetta, R., Barillà, A., et al. (2014). Physical performance and clinical outcomes in dialysis patients: a secondary analysis of the EXCITE trial. *Kidney Blood Press. Res.* 39, 205–211. doi: 10.1159/000355798

van Vilsteren, M. C. B. A., de Greef, M. H. G., and Huisman, R. M. (2005). The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. *Nephrol. Dial. Transplant.* 20, 141–146. doi: 10.1093/ndt/gfh560

Ware, J. E., and Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. *Med. Care* 30, 473–483. doi: 10.1097/00005650-199206000-00002

Yan, X., Eynon, N., Papadimitriou, I. D., Kuang, J., Munson, F., Tirosh, O., et al.' (2017). The gene SMART study: method, study design, and preliminary findings. *BMC Genomics* 18:821. doi: 10.1186/s12864-017-4186-4184

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Effects of intradialytic neuromuscular electrical stimulation in people receiving haemodialysis

With the aim of assessing the effects of the application of NMES during hemodialysis sessions in patients with ESRD, we performed a systematic review and meta-analysis that was published in the *Journal of Physiotherapy* (impact factor 5.551, position 1/65, category: Rehabilitation). Our findings show that intradialytic NMES is effective for improving different markers of functional capacity and muscle strength. A graphical abstract of this study is shown in **Figure 8.**

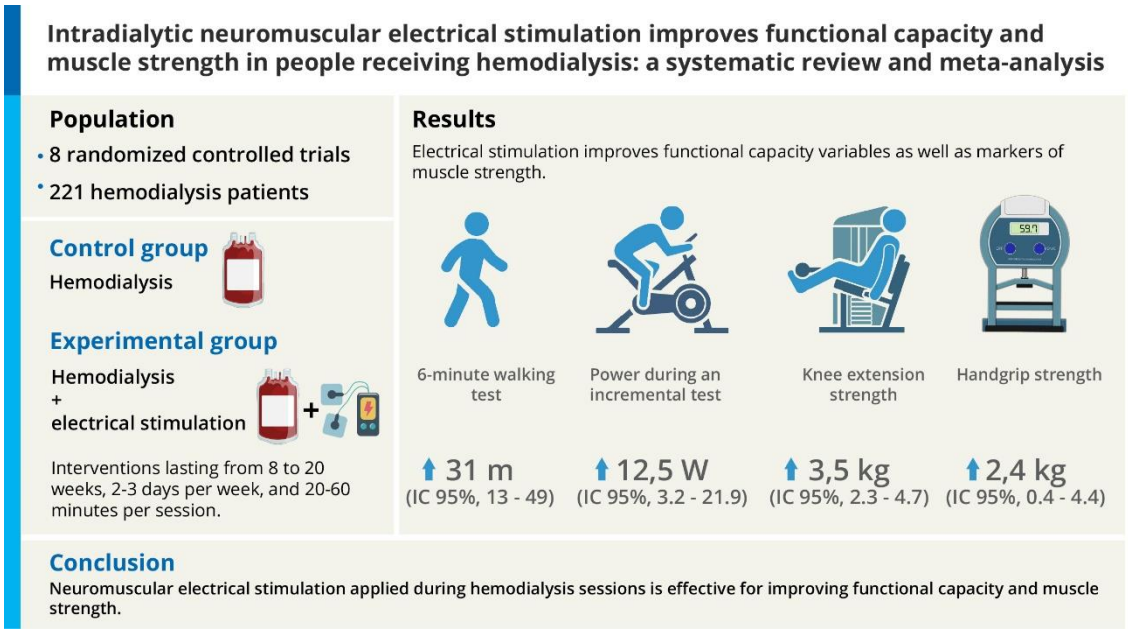


Figure 8. Summary of the effects of intradialytic neuromuscular electrical stimulation in patients receiving hemodialysis.

Journal of Physiotherapy 66 (2020) 89–96

AUSTRALIAN PHYSIOTHERAPY ASSOCIATION

Journal of PHYSIOTHERAPY

journal homepage: www.elsevier.com/locate/jphys

Research

Intradialytic neuromuscular electrical stimulation improves functional capacity and muscle strength in people receiving haemodialysis: a systematic review

Pedro L Valenzuela [a,b], Javier S Morales [c], Luis M Ruilope [d], Pedro de la Villa [a,e], Alejandro Santos-Lozano [d,f], Alejandro Lucia [c,d,g]

[a] *Department of Systems Biology, University of Alcalá;* [b] *Department of Sport and Health, Spanish Agency for Health Protection in Sport (AEPSAD);* [c] *Faculty of Sport Sciences, Universidad Europea de Madrid;* [d] *Hypertension Unit and Cardiorenal Translational Laboratory, Research Institute of the Hospital 12 de Octubre ("imas12"), Madrid;* [e] *Ramón y Cajal Health Research Institute (IRYCIS), Madrid;* [f] *i+HeALTH, Department of Health Sciences, European University Miguel de Cervantes, Valladolid;* [g] *Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain*

KEY WORDS

Neuromuscular electrical stimulation
Muscle atrophy
Exercise training
Haemodilysis
Chronic kidney disease
Physical therapy

ABSTRACT

Questions: Does neuromuscular electrical stimulation (NMES) applied during haemodialysis sessions improve functional capacity in people with end-stage renal disease? Does NMES used in this way also improve muscle strength, muscle mass/architecture, psychological outcomes, cardiovascular outcomes and biochemical variables? Does it have any adverse effects? **Design**: Systematic review of randomised controlled trials with meta-analysis. PubMed, Web of Science, Scopus and SPORTDiscus were searched from inception to 15 October 2019. **Participants**: Patients receiving haemodialysis for end-stage renal disease. **Intervention**: NMES administered during haemodialysis sessions versus control. **Outcomes measures**: Functional capacity, muscle strength, muscle mass, psychological outcomes, cardiovascular outcomes, biochemical variables and adverse events. **Data analysis**: Data were meta-analysed where possible and results were expressed as the pooled mean difference between groups with a 95% confidence interval. **Results**: Eight studies (221 patients) were included in the analysis. Overall, the methodological quality of the studies was fair to good. NMES improved functional capacity as assessed by the 6-minute walk distance test (MD 31 m, 95% CI 13 to 49) and peak workload attained in incremental exercise (MD 12.5 W, 95% CI 3.2 to 21.9). NMES increased knee extensor muscle strength (MD 3.5 kg, 95% CI 2.3 to 4.7) and handgrip strength (MD 2.4 kg, 95% CI 0.4 to 4.4). Muscle mass/architecture was not substantially affected. NMES was estimated to be beneficial for several domains of quality of life in several studies, although most of these estimates were imprecise. No benefits were found for cardiovascular outcomes. The available data did not establish any clear effects on cardiovascular outcomes or biochemical variables (dialysis efficiency, urea and creatinine). No major NMES-related adverse events were observed. **Conclusions**: NMES is safe, practical and effective for improving functional capacity and muscle strength in haemodialysis patients. Further research is needed to confirm the clinical relevance of these findings. **Registration**: PROSPERO CRD42018107323. **[Valenzuela PL, Morales JS, Ruilope LM, de la Villa P, Santos-Lozano A, Lucia A (2020) Intradialytic neuromuscular electrical stimulation improves functional capacity and muscle strength in people receiving haemodialysis: a systematic review. *Journal of Physiotherapy* 66:89–96]**

Introduction

The number of patients treated with haemodialysis for end-stage renal disease (ESRD) is increasing rapidly.[1] Haemodialysis is associated with a marked deterioration of functional capacity,[2,3] which in turn is one of the strongest predictors of mortality in this patient population.[4–9] Therefore, it is important for these patients to maintain an optimal physical state. The level of daily physical activity of haemodialysis patients is overall lower than that of their healthy peers,[10] especially on dialysis days.[11] In this regard, the inclusion of intradialytic exercise programs has proven to be effective for improving patients' functional capacity.[12–15] However, voluntary exercise is not always feasible for these patients because of very poor physical status in some cases and logistical limitations in general (eg, some patients may find it difficult to perform exercise while seated in a semi-recumbent position during haemodialysis sessions).

Several non-pharmacological strategies are used to prevent the functional decline that accompanies periods of forced physical inactivity, such as those imposed by haemodialysis.[16] In this context, neuromuscular electrical stimulation (NMES), which is the application of intermittent electrical stimuli to generate involuntary muscle contractions, might serve as an 'exercise mimetic'. Meta-analytical evidence indicates that NMES is an effective strategy against muscle weakness in populations at high risk of muscle disuse such as

https://doi.org/10.1016/j.jphys.2020.03.006

Box 1. Inclusion criteria.

Design
- Randomised or quasi-randomised trial
- English or Spanish language

Participants
- People undergoing haemodialysis

Intervention
- Intradialytic neuromuscular electrical stimulation
- Treatment period > 4 weeks

Outcome measures
- Functional capacity
- Muscle strength
- Muscle mass/architecture
- Psychological outcomes (eg, quality of life)
- Cardiovascular outcomes (eg, flow-mediated dilation)
- Biochemical variables (eg, dialysis efficiency, urea and creatinine)
- Adverse events

Comparisons
- Intradialytic neuromuscular electrical stimulation versus no intervention

critically ill patients or adults with advanced disease.[17,18] NMES has also been proven to improve muscle strength and functionality in different clinical populations, including pre-frail and long-stay hospitalised elderly individuals.[19–21] Thus, NMES training appears to be a feasible and effective strategy with which to combat muscle disuse atrophy and muscle function decline in people with difficulties performing volitional exercise.[22–24]

Several studies have also demonstrated that NMES can be performed during haemodialysis sessions.[25–29]

Therefore, the research questions for this systematic review were:

1. Does neuromuscular electrical stimulation (NMES) applied during haemodialysis sessions improve functional capacity in people with end-stage renal disease?
2. Does NMES used in this way also improve muscle mass/architecture, quality of life and biochemical variables?
3. Does it have any adverse effects?

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Identification and selection of studies

PubMed, Web of Science, Scopus and SPORTDiscus were searched from inception to 15 October 2019 with the search terms: dialy* AND ("electrical stimulation" OR electrostimulation OR NMES OR "electro stimulation"). The electronic search was supplemented with a manual review of reference lists from relevant publications and reviews to locate additional publications on the subject. Grey literature (eg, abstracts, conference proceedings and editorials) and reviews were excluded. Two authors (PLV and JSM) independently screened the titles and abstracts and then evaluated the full text of potentially relevant studies. Disagreements were resolved through discussion with a third author (ASL). Studies were eligible for inclusion if they met the eligibility criteria presented in Box 1. The control group (ie, haemodialysis patients not receiving NMES) could not receive any other type of physical strategy (eg, massage, exercise) during the haemodialysis sessions.

Assessment of characteristics of the studies

Two authors (PLV and JSM) independently extracted the following data from the studies. Any disagreements were resolved through discussion with a third author (ASL).

Quality

The methodological quality of the included studies was assessed with the PEDro scale, which is based on the Delphi list.[30] The 10 PEDro scale criteria that contribute to the total score between 0 and 10 are presented in Table 1. Each study's quality was further categorised as poor (PEDro score < 3), fair (4 to 5) or good (> 5).

Participants

The following data were extracted from each study, if available: number of participants within each group, participants' mean age, aetiology of ESRD and number of years on haemodialysis.

Intervention

The following NMES intervention characteristics were extracted from each study: frequency, pulse width, on:off ratio, current, session duration, number of sessions per week and duration of treatment period.

Outcome measures

The measurement methods and outcome data (ie, mean and standard deviation for each group) were extracted for the following outcome measures from each study, if available: functional capacity (eg, walking ability), muscle strength, muscle mass/architecture, psychological outcomes (eg, quality of life), cardiovascular outcomes (eg, flow-mediated dilation) and biochemical variables (eg, dialysis

Table 1
PEDro scores of included studies.

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15% dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0 to 10)
Dobsak et al (2012)[26]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Esteve-Simó et al (2015)[29]	N	N	Y	N	N	N	Y	N	Y	Y	4
Esteve-Simó et al (2017)[28]	N	N	Y	N	N	N	Y	N	Y	Y	4
McGregor et al (2018)[31]	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Miura et al (2018)[34]	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Roxo et al (2016)[25]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Schardong et al (2017, 2018)[27,32]	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Suzuki et al (2018)[33]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7

efficiency, urea and creatinine). Data about adverse events were also extracted. Authors were contacted, when necessary, to clarify any uncertainty or to request additional data. Although psychological, cardiovascular and biochemical measures were not registered outcomes, substantial amounts of data were identified, so they are reported here as non-registered outcomes.

Data analysis

A meta-analysis was performed when at least two studies estimated the effect of NMES by comparing the experimental and control groups on a given endpoint. The weighted mean difference (WMD) between interventions (post-intervention *minus* pre-intervention data) and 95% CI were computed using a random-effects model. When studies reported a given endpoint in different and non-combinable units, the standardised mean difference (SMD) was used for analyses. The correlation coefficient (Pearson's *r*) between pre-intervention and post-intervention data were entered to compute the within-group SD. The authors of four papers provided the requested *r*-value.[25,28,29,31] A conservative *r*-value of 0.7 was used when Pearson's *r* was unknown, and a sensitivity analysis (r = 0.2, 0.5 or 0.9) was performed to confirm the results. Begg's test was used to determine the presence of publication bias (unless the number of studies analysing the outcome in question was lower than three), and the Q and I^2 statistics were used to assess heterogeneity across studies. The level of significance was set at 0.05. All statistical analyses were performed using a commercial statistical software package[a].

Results

Flow of studies through the review

From the retrieved articles, eight trials reported in nine papers and including a total of 221 dialysis participants (118 in the experimental arms) met all inclusion criteria and were included in the systematic review (Figure 1). Two papers reported data from the same study,[27,32] and thus only one was used to count the total number of subjects.

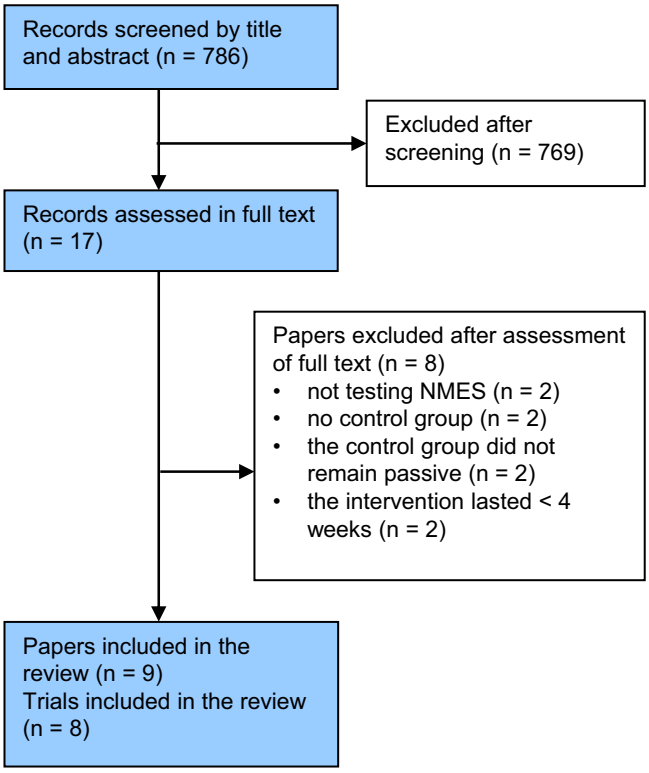


Figure 1. Flow of studies through the review. Papers may have been ineligible for failing to meet more than one inclusion criteria.
NMES = neuromuscular electrical stimulation.

Characteristics of the included studies

Quality

The total PEDro score for each study and the ratings on the 10 criteria that contributed to that total score are presented in Table 1. All studies were included in the review regardless of their quality. Two studies had a total score of 6 to 7 (good quality). The sample size of the included studies was low, with the largest study including 23 participants in the experimental arm.[29]

Participants

The characteristics of the included studies are summarised in Table 2. Most studies analysed male and female participants with a mean age > 60 years (with a maximum mean value of 73 years), although two studies analysed subjects whose mean age ranged between 45 and 55 years.[25,31] Participants had been on haemodialysis for a mean of 2 to 11 years. The major aetiologies of ESRD were diabetic nephropathy, glomerulonephritis, polycystic kidney disease and hypertension.

Intervention

The duration of the NMES interventions ranged from 8 weeks[25,27,32,33] to 20 weeks.[26] NMES was performed two to three times per week in all studies and was applied over the quadriceps muscles, although two studies also stimulated the calf muscles,[26,34] another study stimulated the hamstrings[31] and a further study stimulated the whole legs.[33] NMES sessions lasted between 20 and 60 minutes. Rectangular pulses (range 200 to 400 μs) were applied in all cases. Three studies applied a low-frequency stimulation (5 to 20 Hz),[26,31,33] two studies applied a moderate to high frequency (50 to 80 Hz)[25,27,32] and three studies progressively increased stimulation frequency during the intervention period.[28,29,34] With regard to stimulation intensity, four studies applied the highest tolerable intensity in each session,[25,27,31–33] one study progressively increased the intensity up to 60 mA during the intervention period[26] and three studies did not report the stimulation intensity.[28,29,34]

Effect of intervention

Functional capacity

Outcome data related to functional capacity was reported in all but two of the included studies.[25–29,31,33] NMES improved the 6-minute walk distance by a mean of 31 m (95% CI 13 to 49), with no signs of heterogeneity (I^2 = 0, Q = 1.308) or publication bias (p = 0.500). The meta-analysis for this result is presented in Figure 2, with a detailed forest plot presented in Figure 3 on the eAddenda. The sensitivity analysis confirmed the benefits when entering an *r*-value of 0.2 (MD 31 m, 95% CI 12 to 50), 0.5 (MD 31 m, 95%CI 13 to 49) or 0.9 (SMD 31 m, 95% CI 16 to 47).

Three studies also analysed performance during different variants of the sit-to-stand (STS) test, with two measuring the time needed to perform 10 repetitions (STS-10)[28,29] and the other reporting the maximum number of repetitions performed in 30 seconds.[27] The best estimate was that NMES improved results on the STS test, with a standardised mean difference of 0.42. However, this estimate was associated with considerable uncertainty, with a 95% CI spanning from −0.04 to 0.87. There were no signs of heterogeneity (I^2 = 0, Q = 0.05) or publication bias (p = 0.5). The meta-analysis for this result is presented in Figure 4, with a detailed forest plot presented in Figure 5 on the eAddenda. The sensitivity analysis showed significant benefits when entering an *r*-value of 0.9 (SMD 0.50, 95% CI 0.04 to 0.96), but not with an *r*-value of 0.2 (SMD 0.36, 95% CI −0.09 to 0.82) or 0.5 (SMD 0.39, 95% CI −0.07 to 0.84). When the two studies that assessed the STS test using the same procedures (ie, STS-10) were pooled, on average NMES reduced the time required to complete 10 repetitions (MD −5.9 seconds) but this estimate was again associated with important uncertainty (95% CI −14.5 to 2.7, Q = 0.222 and I^2 = 0).

Table 2
Summary of included studies.

Study	Design	Participants	Intervention	Outcome measures
Dobsak et al (2012)[26]	RCT	n = 21 Mean age (*yr*) = Exp 60, Con 65	Exp = NMES: 10 Hz, 200 μs, 20 s on:20 s off increasing up to 60 mA 60 min × 3/wk × 20 wk Con = no intervention	• Cycle ergometry Wpeak • 6-MWD • Knee extension strength • Quality of life • Biochemical analyses
Esteve-Simó et al (2015)[29]	QRCT	n = 38 Mean age (*yr*) = Exp 73, Con 68	Exp = NMES: 8 to 90 Hz, 5.5 s to 25 min on:0.75 to 1.5 s off intensity not reported. 25 to 38 min × 3/wk × 12 wk Con = no intervention	• 6-MWD • STS-10 • Knee extension strength • Handgrip strength • Biochemical analyses • Muscle area • Quality of life
Esteve-Simó et al (2017)[28]	QRCT	n = 20 Mean age (*yr*) = Exp 72, Con 66	Exp = NMES: 8 to 90 Hz, 5.5 s to 25 min on:0.75 to 1.5 s off intensity not reported. 25 to 38 min × 3/wk × 12 wk Con = no intervention	• 6-MWD • STS-10 • Knee extension strength • Handgrip strength • Biochemical analyses • Muscle area
McGregor et al (2018)[31]	RCT	n = 35 Mean age (*yr*) = Exp 52, Con 54	Exp = NMES: 5 Hz, 760 to 857 μs, and variable stimulation time highest tolerable intensity 1 hr × 3/wk × 10 wk Con = no intervention	• Cycle ergometry Wpeak • Knee extension strength • Handgrip strength • Biochemical analyses
Miura et al (2018)[34]	RCT	n = 20 Mean age (*yr*) = Exp 69, Con 70	Exp = NMES: 10 Hz < pain threshold, 20 s on:20 s off intensity not reported. < 1 hr × 2/wk × 12 wk Con = no intervention	• Knee extension strength • Handgrip strength • Biochemical analyses
Roxo et al (2016)[25]	RCT	n = 40 Mean age (*yr*) = Exp 46, Con 55	Exp = NMES: 50 Hz, 350 μs, 2 s on:10 s off highest tolerable intensity 30 min × 3/wk × 8 wk Con = no intervention	• 6-MWD • Knee extension strength • Biochemical analyses
Schardong et al (2017, 2018)[27,32]	RCT	n = 21 Mean age (*yr*) = Exp 59, Con 64	Exp = NMES: 80 Hz, 400 μs, 10 s on:50 to 20 s off highest tolerable intensity 20 to 34 min × 3/wk × 8 wk Con = no intervention	• 6-MWD • Knee extension strength • Quadriceps architecture • DNA damage
Suzuki et al (2018)[33]	RCT	n = 26 Mean age (*yr*) = Exp 66, Con 65	Exp = NMES: 20 Hz, 250 μs, 5 s on:2 s off highest tolerable intensity 20 min × 3/wk × 8 wk Con = no intervention	• TUG test • Knee extension strength • Quadriceps muscle area • Biochemical analyses • Quality of life

Con = control group, DNA = deoxyribonucleic acid, Exp = experimental group, NMES = neuromuscular electrical stimulation, QRCT = quasi-randomised controlled trial, RCT = randomised controlled trial, STS = sit-to-stand test, TUG = Timed Up and Go test, Wpeak = peak power, 6-MWD = 6-minute walk distance.

Two studies analysed the effect of NMES on peak workload during a cycling incremental test, and pooled analyses showed a clear improvement over the control group (MD 12.5 W, 95% CI 3.2 to 21.9; Q = 1.000 and I^2 = 0). Results were similar in sensitivity analyses (for *r* = 0.2: SMD 14.8 W, 95% CI 7.5 to 22.0; for *r* = 0.5: SMD 13.8 W, 95% CI 5.6 to 22.0; and for *r* = 0.9: SMD 11.3 W, 95% CI 1.5 to 21.0).

One further study[31] reported intervention-induced improvements in the peak oxygen uptake (VO_{2peak}) attained during an incremental test compared with the control group (2.0 ml/kg/min, 95% CI 0.3 to 3.7) and another study[33] reported improvements in the Timed Up and Go test (ie, reduction in the time needed to accomplish the test) with NMES compared with the control group (MD −1.00 seconds, 95% CI −1.45 to −0.55).

Muscle strength

Eight studies analysed the effects of NMES on the strength of the knee extensors.[25–29,31,33,34] Seven of these studies assessed the strength of the knee extensors using isometric dynamometry,[26–29,31,33,34] with pooled analysis showing a benefit (MD 3.5 kg, 95% CI 2.3 to 4.7). The meta-analysis for this result is presented in Figure 6, with a detailed forest plot presented in Figure 7 on the eAddenda. This effect was still present when entering an *r*-value of 0.2 (MD 3.4 kg, 95% CI 2.2 to 4.7), 0.5 (MD 3.5 kg, 95% CI 2.3 to 4.7) or 0.9 (MD 3.6 kg, 95% CI 2.6 to 4.6). The other study assessed knee extensor muscle strength with the one-repetition maximum test and also estimated that NMES was beneficial compared with no intervention (MD 1.7 kg, 95% CI 1.1 to 2.3).[25]

Three studies[28,29,34] measured handgrip strength. Pooled analysis showed greater benefit with NMES compared with the control (MD 2.4 kg, 95% CI 0.4 to 4.4). The meta-analysis for this result is presented in Figure 8, with a detailed forest plot presented in Figure 9 on the eAddenda. No heterogeneity (Q = 1.631 and I^2 = 0) or publication bias

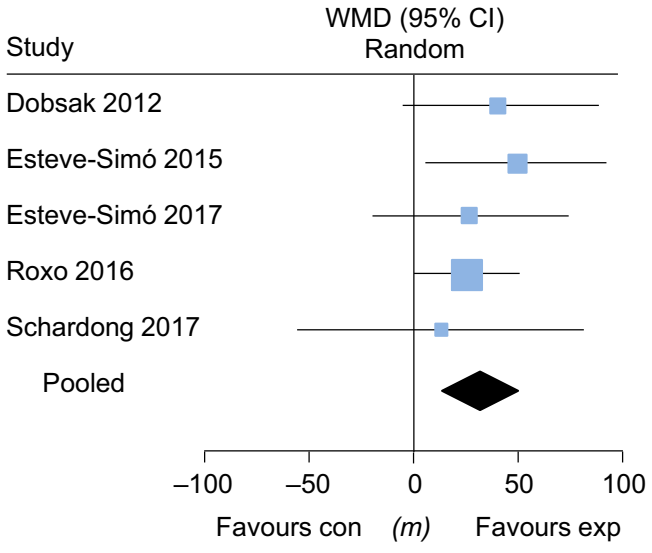


Figure 2. Weighted mean difference (95% CI) of effect of neuromuscular electrical stimulation on the 6-minute walk distance.

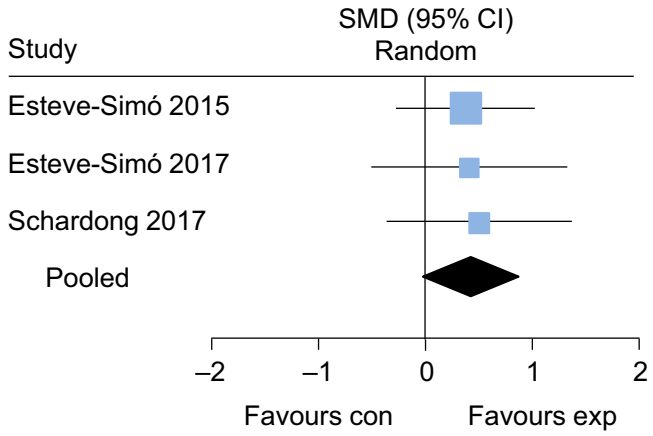


Figure 4. Standardised mean difference (95% CI) of effect of neuromuscular electrical stimulation on the sit-to-stand test.

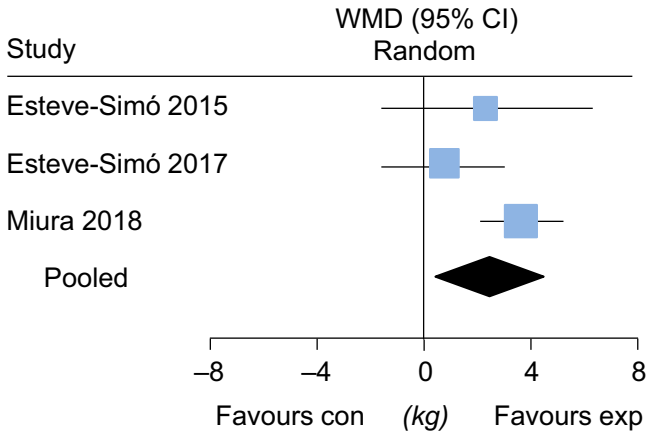


Figure 8. Weighted mean difference (95% CI) of effect of neuromuscular electrical stimulation on handgrip strength.

(p = 0.500) were evident. Benefit from NMES was also evident in the sensitivity analyses (for r = 0.2: MD 2.1 kg, 95% CI 0.2 to 4.0; for r = 0.5: MD 2.3 kg, 95% CI 0.3 to 4.2; and for r = 0.9: MD 2.5 kg, 95% CI 0.4 to 4.5).

One study found that NMES had a beneficial effect on respiratory muscle strength, estimating its effect on maximal inspiratory pressure at 12 cmH_2O (95% CI 3 to 21). The mean estimate of the effect on maximal expiratory pressure was also beneficial (MD 9 cmH_20), although this was an uncertain estimate (95% CI –1 to 18).[25]

Muscle mass and architecture

Three studies analysed the quadriceps muscle area,[28,29,33] producing an unclear estimate of the effect of NMES over the control (MD 3.5 cm^2, 95% CI –1.6 to 8.6, I^2 = 0, Q = 0.850, and Begg's test p = 0.500). One study assessed muscle thickness and architecture by ultrasonography, finding an increased pennation angle but no improvements in muscle thickness.[27]

Psychological outcomes

Three studies analysed the effects of NMES on quality of life.[28,29,33] One used the 36-item short-form health survey questionnaire and estimated the effect of NMES on mental function component score at 6.2 (95% CI 1.6 to 10.8). This study also estimated that the effect of NMES on the physical component was beneficial (MD 4.3), although this estimate was uncertain (95% CI –0.4 to 9.0).[26] Another study assessed quality of life with the EuroQoL-5D questionnaire.[29] It estimated that the effect of NMES on the health visual scale was beneficial (MD 8.1), but this was again associated with uncertainty (95% CI –1.0 to 17.2). This latter study also estimated that NMES decreases lower limb symptoms (ie, muscular pain, cramps, tingling, burning/stinging and numbness) by a mean of 2.7 on the 0 to 25 symptom scale (95% CI 1.2 to 4.2). A further study used the eight-item short form health survey questionnaire; although the estimated effect of NMES on some domains (such as physical function) was favourable compared with no intervention, the estimates were too imprecise to confirm this.[33]

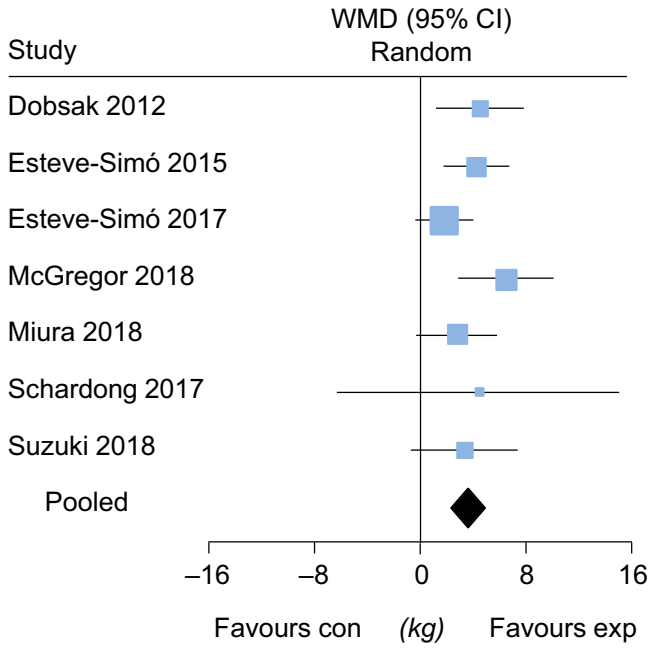


Figure 6. Weighted mean difference (95% CI) of effect of neuromuscular electrical stimulation on the strength of the knee extensors.

Cardiovascular outcomes

Two studies analysed cardiovascular-related outcomes.[27,31] Pooled analysis showed no clear effects on flow-mediated dilation (MD 0.11%, 95% CI –1.29 to 1.52, I^2 = 0 and Q = 0.001). No other outcome could be meta-analysed, but no significant effects were reported by the authors of these two studies for any of outcomes they assessed (left ventricular mass index, ejection fraction or end-diastolic volume, left atria diameter, blood pressure or pulse wave velocity).

Biochemical outcomes

Six of the nine studies performed biochemical analysis before and after the intervention.[25,26,28,29,33,34] No clear effects were observed in major biochemical parameters such as Kt/V ratio (MD 0.03, 95% CI –0.19 to 0.26, I^2 = 0, Q = 2.189 and Begg's test p = 0.231) or serum C-reactive protein (MD –0.03 mg/dl, 95% CI –0.12 to 0.06, I^2 = 0, Q = 1.908 and Begg's test p = 0.500), albumin (MD –0.04, 95% CI –0.15 to 0.08, I^2 = 0, Q = 2.796 and Begg's test p = 0.367) and creatinine concentration (SMD 0.26, 95% CI –0.15 to 0.66, I^2 = 0, Q = 1.449 and Begg's test p = 0.5).

Adverse events

The prevalence of NMES-related adverse events was reported in all studies.[25–29,31–34] Most reported no NMES-related adverse events, but in one study there were two drop-outs (10% of participants) caused by intolerance to the NMES intervention.[31] In another study one participant (8%) had leg cramps during an NMES session, which rapidly disappeared without treatment.[33] A further three participants (23%) reported muscle pain immediately after at least one training session and recovered without treatment in a few days.[33] One study examined a recognised adverse effect of haemodialysis: DNA damage. This study reported reductions in DNA damage associated with the NMES intervention.[32]

Discussion

The main finding of this systematic review is that NMES applied during haemodialysis visits (30 to 60 minutes, three times per week) might represent an overall safe and effective strategy for the improvement of patients' muscle strength and functional capacity. Preliminary evidence also indicates that intradialytic NMES could increase quality of life in this patient population. No substantial

benefits were observed for muscle mass, or for cardiovascular and biochemical outcomes.

The potential of NMES to improve muscle strength in clinical practice has been highlighted previously, particularly in those individuals with difficulties performing volitional exercise.[22–24] NMES has been proposed as an 'exercise mimetic' because of its ability to activate the same signalling pathways as those stimulated by voluntary exercise.[35] Moreover, because NMES induces a synchronised recruitment of muscle fibres independent of their contractile/metabolic phenotype, it can also mimic the effect of high-intensity exercise in terms of recruitment of 'fast-twitch' fibres.[36] NMES also increases muscle oxidative capacity and improves functional endurance, especially in clinical patient populations.[37] Although it was traditionally believed that NMES bypasses the central nervous system, it is now established that, similar to voluntary contractions, electrically evoked muscle contractions elicit the activation of corticomotor pathways.[38,39] Accordingly, NMES has the potential to promote beneficial adaptations both at the peripheral and central nervous system levels, and indeed this strategy has been reported to improve neural activation.[40]

In agreement with previous findings in a variety of clinical populations at risk of muscle weakness (critically ill patients, individuals with advanced disease, pre-frail elderly subjects),[17–20] the current results generally indicate that NMES might represent an effective strategy with which to improve strength and functional ability in haemodialysis patients. Specifically, NMES seemed to improve 6-minute walk distance, peak workload during incremental exercise, handgrip and lower-limb muscle strength (as reflected by greater knee extensor muscle strength), with the latter being an important finding because poor levels of both handgrip and lower-limb strength are associated with risk of mortality, cardiovascular events and hospitalisation in haemodialysis patients.[7,8,41,42] These results tend to support the routine implementation of NMES in clinical practice because it may not only attenuate dialysis-associated physical impairment, but also reduce patients' morbimortality risk. It must be noted, however, that the improvements estimated for the 6-minute walk distance (95% CI 13 to 49 m) and handgrip strength (95% CI 0.4 to 4.4 kg) are mostly lower than the minimal detectable change previously reported by other authors for this patient population (57 to 66 m and 3.0 to 3.4 kg, respectively).[14,43] Moreover, the minimal important differences for other outcomes assessed here (knee extensor muscle strength, peak workload) remain to be clarified. Thus, in line with the trend previously observed with voluntary exercise training for haemodialysis patients,[14] these results indicate that patients do generally benefit from NMES, but future research should seek to refine these estimates in order to determine to what extent the benefits are clinically worthwhile. Future research could also seek to identify those patients who are likely to obtain the greatest benefits.

It has been reported that, compared with muscle strength and functional performance, muscle mass might not be a useful health marker in haemodialysis patients.[44,45] However, given the importance of muscle mass for health in all populations[46] and its protective role against cardiometabolic conditions, especially in ageing populations,[47] is important to develop interventions that attenuate muscle wasting in haemodialysis patients. In this regard, the current results show no clear benefit of NMES on the promotion of muscle anabolism. Ageing has been related to skeletal muscle anabolic resistance, and periods of inactivity (such as those imposed by dialysis) result in further anabolic impairment.[48,49] Given the age of the participants included in this review (mean of 60+ years in most studies), NMES or other physical exercise strategies should perhaps be accompanied by an optimal amino acid intake, in order to effectively promote muscle anabolism in this population.[49,50] Limitations of the measurement methods could also partly explain the lack of benefits on muscle mass. Indeed, three of the included studies assessed changes in muscle area through magnetic resonance imaging[33] or the analysis of limb circumference and skinfold thickness,[28,29] and the other study assessed muscle area by ultrasonography.[27] Although dialysis patients usually present with measures of total muscle cross-sectional area (CSA) comparable with those of healthy peers, their contractile tissue CSA is smaller.[51] Therefore, more accurate methods such as magnetic resonance imaging or dual-energy X-ray absorptiometry might be required to properly discern changes in actual muscle contractile CSA in these patients. In this regard, NMES increases type II muscle fibre CSA in older people,[21] and the only study included in the present meta-analysis that assessed quadriceps' CSA through magnetic resonance imaging found significant benefits with NMES over the control group.[33]

This review also evaluated whether NMES could induce changes in dialysis-related biochemical parameters such as Kt/V or serum C-reactive protein, creatinine and albumin. Physical exercise increases blood flow through the working muscles, thus facilitating the diffusion of waste products towards the circulatory system. Previous research has demonstrated that intradialytic exercise improves haemodialysis efficacy (as reflected by increases in markers of urea clearance such as Kt/V)[15,52–54] and the current review therefore assessed whether NMES could elicit similar benefits. However, no significant changes in these parameters were found, which could be due, at least in part, to the low volume of muscle mass recruited during NMES (involving only local stimulation of the quadriceps muscles). We also found no changes in other biochemical markers such as C-reactive protein, serum creatinine and albumin, which suggests that NMES does not induce changes in the inflammatory status or renal function.

Although the present results partly support the routine implementation of NMES during dialysis sessions, it is acknowledged that voluntary physical exercise should be performed whenever possible. The application of NMES superimposed onto voluntary physical exercise could provide greater benefits than the latter alone in clinical populations,[55] and might be an effective strategy for maximising training stimuli and subsequent muscle adaptations in patients who can perform volitional exercise.[14] Future research might determine the efficacy of NMES superimposed onto voluntary physical exercise in ESRD patients.

The quality of the included studies was generally fair to good, but some limitations need to be mentioned. Two studies followed a quasi-randomised design, and the sample size of all the included studies was overall low (consistently < 23 participants in the NMES arm). Moreover, no blinding of participants (which is difficult to achieve with NMES) or of the researchers in charge of NMES application and of outcome assessment was performed in most studies, and therefore a placebo effect and a potential performance and detection bias cannot be ruled out. Further research, especially long-term randomised controlled trials, will be needed to confirm the effectiveness and safety of NMES in dialysis patients.

In conclusion, intradialytic NMES (30 to 60 minutes per session, two to three times weekly) appears to be a safe and effective strategy for improving muscle strength and functional capacity in patients with ESRD. Preliminary evidence also suggests that it may improve quality of life, but no consistent benefits have been reported for muscle mass, or cardiovascular and biochemical outcomes (Kt/V and serum creatinine, urea, albumin and C-reactive protein). These results partly support the implementation of NMES during dialysis sessions when volitional exercise cannot be easily performed, but further research is needed to confirm the clinical relevance of these results.

What was already known on this topic: Haemodialysis is being used to manage the growing number of people with end-stage renal disease. Haemodialysis is associated with a marked deterioration of functional capacity. Voluntary exercise is not always feasible for these patients.

What this study adds: Intradialytic neuromuscular electrical stimulation improves functional capacity and muscle strength. It also appears to improve some aspects of quality of life. No clear effects on cardiovascular or biochemical outcomes were identified, but it can be delivered without adverse effects.

Footnotes: [a] Comprehensive Meta-analysis 2.0, Biostat, Englewood, USA.

eAddenda: Figures 3, 5, 7 and 9 can be found online at https://doi.org/10.1016/j.jphys.2020.03.006.

Ethics approval: Not applicable.

Competing interest: The authors declare no conflicts of interest.

Sources of support: PLV is supported by a predoctoral contract granted by the University of Alcalá (FPI2016). JSM is supported by a predoctoral contract granted by the Ministry of Education, Culture and Sport (FPU14/03435). AL is supported by grants from the Spanish Ministry of Science and Innovation (Fondo de Investigaciones Sanitarias, grant number PI15/00558 and PI18/00139).

Acknowledgements: Nil.

Author contributions: PLV and AL conceived and designed the study. PLV and JSM performed the systematic search. PLV and ASL performed all statistical analyses. All authors contributed to data analysis and interpretation. PLV and AL drafted the manuscript, and all authors contributed to and approved the final version to be published.

Provenance: Not invited. Peer reviewed.

Correspondence: Alejandro Lucia, Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain. Email: alejandro.lucia@universidadeuropea.es

References

1. Szczech LA, Lazar IL. Projecting the United States ESRD population: issues regarding treatment of patients with ESRD. *Kidney Int Suppl*. 2004;66:S3–S7.
2. Leal VO, Stockler-Pinto MB, Farage NE, Aranha LN, Fouque D, Anjos LA, et al. Handgrip strength and its dialysis determinants in hemodialysis patients. *Nutrition*. 2011;27:1125–1129.
3. Painter P. Physical functioning in end-stage renal disease patients: update 2005. *Hemodial Int*. 2005;9:218–235.
4. O'Hare AM, Tawney K, Bacchetti P, Johansen KL. Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2. *Am J Kidney Dis*. 2003;41:447–454.
5. Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int*. 2004;65:719–724.
6. Stack AG, Molony DA, Rives T, Tyson J, Murthy BVR. Association of physical activity with mortality in the US dialysis population. *Am J Kidney Dis*. 2005;45:690–701.
7. Roshanravan B, Robinson-Cohen C, Patel KV, Ayers E, Littman AJ, de Boer IH, et al. Association between Physical Performance and All-Cause Mortality in CKD. *J Am Soc Nephrol*. 2013;24:822–830.
8. Torino C, Manfredini F, Bolignano D, Aucella F, Baggetta R, Barillà A, et al. Physical performance and clinical outcomes in dialysis patients: a secondary analysis of the excite trial. *Kidney Blood Press Res*. 2014;39:205–211.
9. Morishita S, Tsubaki A, Shirai N. Physical function was related to mortality in patients with chronic kidney disease and dialysis. *Hemodial Int*. 2017;21:483–489.
10. Johansen KL, Chertow GM, Kutner NG, Dalrymple LS, Grimes BA, Kaysen GA. Low level of self-reported physical activity in ambulatory patients new to dialysis. *Kidney Int*. 2010;78:1164–1170.
11. Majchrzak KM, Pupim LB, Chen K, Martin CJ, Gaffney S, Greene JH, et al. Physical activity patterns in chronic hemodialysis patients: comparison of dialysis and nondialysis days. *J Ren Nutr*. 2005;15:217–224.
12. Chung Y-C, Yeh M-L, Liu Y-M. Effects of intradialytic exercise on the physical function, depression and quality of life for haemodialysis patients: a systematic review and meta-analysis of randomised controlled trials. *J Clin Nurs*. 2017;26:1801–1813.
13. Smart N, Steele M. Exercise training in haemodialysis patients: a systematic review and meta-analysis. *Nephrology*. 2011;16:626–632.
14. Valenzuela PL, de Alba A, Pedrero-Chamizo R, Morales JS, Cobo F, Botella A, et al. Intradialytic exercise: one size doesn't fit all. *Front Physiol*. 2018;9:844.
15. Scapini KB, Bohlke M, Moraes OA, Rodrigues CG, Inácio JF, Sbruzzi G, et al. Combined training is the most effective training modality to improve aerobic capacity and blood pressure control in people requiring haemodialysis for end-stage renal disease: systematic review and network meta-analysis. *J Physiother*. 2019;65:4–15.
16. Valenzuela PL, Morales JS, Pareja-Galeano H, Izquierdo M, Emanuele E, de la Villa P, et al. Physical strategies to prevent disuse-induced functional decline in the elderly. *Ageing Res Rev*. 2018;47:80–88.
17. Jones S, Man William DC, Gao W, Higginson Irene J, Wilcock A, Maddocks M. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane Database Syst Rev*. 2016;10:CD009419.
18. Burke D, Gorman E, Stokes D, Lennon O. An evaluation of neuromuscular electrical stimulation in critical care using the ICF framework: a systematic review and meta-analysis. *Clin Respir J*. 2016;10:407–420.
19. Maggioni MA, Cè E, Rampichini S, Ferrario M, Giordano G, Veicsteinas A, et al. Electrical stimulation versus kinesitherapy in improving functional fitness in older women: a randomized controlled trial. *Arch Gerontol Geriatr*. 2010;50:e19–e25.
20. Mignardot JB, Deschamps T, Le Goff CG, Roumier FX, Duclay J, Martin A, et al. Neuromuscular electrical stimulation leads to physiological gains enhancing postural balance in the pre-frail elderly. *Physiol Rep*. 2015;3:1–18.
21. Kern H, Barberi L, Löfler S, Sbardella S, Burggraf S, Fruhmann H, et al. Electrical stimulation counteracts muscle decline in seniors. *Front Aging Neurosci*. 2014;6:1–11.
22. Dirks ML, Wall BT, van Loon LJC. Interventional strategies to combat muscle disuse atrophy in humans: focus on neuromuscular electrical stimulation and dietary protein. *J Appl Physiol*. 2018;125:850–861.
23. Maffiuletti NA, Gondin J, Place N, Stevens-Lapsley J, Vivodtzev I, Minetto MA. Clinical use of neuromuscular electrical stimulation for neuromuscular rehabilitation: what are we overlooking? *Arch Phys Med Rehabil*. 2018;99:806–812.
24. Paillard T. Muscle plasticity of aged subjects in response to electrical stimulation training and inversion and/or limitation of the sarcopenic process. *Ageing Res Rev*. 2018;46:1–13.
25. Roxo RS, Xavier VB, Miorin LA, Magalhães AO, Sens YA, Alves VL. Impact of neuromuscular electrical stimulation on functional capacity of patients with chronic kidney disease on hemodialysis. *J Bras Nefrol*. 2016;38:344–350.
26. Dobsak P, Homolka P, Svojanovsky J, Reichertova A, Soucek M, Novakova M, et al. Intra-dialytic electrostimulation of leg extensors may improve exercise tolerance and quality of life in hemodialyzed patients. *Artif Organs*. 2012;36:71–78.
27. Schardong J, Dipp T, Bozzeto CB, da Silva MG, Baldissera GL, Ribeiro RD, et al. Effects of intradialytic neuromuscular electrical stimulation on strength and muscle architecture in patients with chronic kidney failure: randomized clinical trial. *Artif Organs*. 2017;41:1049–1058.
28. Esteve-Simó V, Carneiro J, Moreno F, Fulquet M, Garriga S, Pou M, et al. The effect of neuromuscular electrical stimulation on muscle strength, functional capacity and body composition in haemodialysis patients. *Nefrologia*. 2017;37:68–77.
29. Esteve-Simó V, Jiménez AJ, Oliveira JC, Guzmán FM, Nicolás MF, Potau MP, et al. Efficacy of neuromuscular electrostimulation intervention to improve physical function in haemodialysis patients. *Int Urol Nephrol*. 2015;47:1709–1717.
30. Verhagen A, de Vet H, de Bie R, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol*. 1998;51:1235–1241.
31. McGregor G, Ennis S, Powell R, Hamborg T, Raymond NT, Owen W, et al. Feasibility and effects of intra-dialytic low-frequency electrical muscle stimulation and cycle training: a pilot randomized controlled trial. *PLoS One*. 2018;13:1–17.
32. Schardong J, Brito V, Dipp T, Macagnan FE, Saffi J, Méa Plentz RD. Intradialytic neuromuscular electrical stimulation reduces DNA damage in chronic kidney failure patients: a randomized controlled trial. *Biomarkers*. 2018;23:495–501.
33. Suzuki T, Ikeda M, Minami M, Matayoshi Y, Nakao M, Nakamura T, et al. Beneficial effect of intradialytic electrical muscle stimulation in hemodialysis patients: a randomized controlled trial. *Artif Organs*. 2018;42:899–910.
34. Miura M, Hirayama A, Oowada S, Nishida A, Saito C, Yamagata K, et al. Effects of electrical stimulation on muscle power and biochemical markers during hemodialysis in elderly patients: a pilot randomized clinical trial. *Ren Replace Ther*. 2018;4:1–8.
35. Atherton PJ, Babraj J, Smith K, Singh J, Rennie MJ, Wackerhage H. Selective activation of AMPK-PGC-1α or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. *FASEB J*. 2005;19:786–788.
36. Bickel CS, Gregory CM, Dean JC. Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal. *Eur J Appl Physiol*. 2011;111:2399–2407.
37. Veldman MP, Gondin J, Place N, Maffiuletti NA. Effects of neuromuscular electrical stimulation training on endurance performance. *Front Physiol*. 2016;7:1–5.
38. Blickenstorfer A, Kleiser R, Keller T, Keisker B, Meyer M, Riener R, et al. Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. *Hum Brain Mapp*. 2009;30:963–975.
39. Francis S, Lin X, Aboushoushah S, White TP, Phillips M, Bowtell R. fMRI analysis of active, passive and electrically stimulated ankle dorsiflexion. *Neuroimage*. 2009;44:469–479.
40. Maffiuletti NA, Pensini M, Martin A. Activation of human plantar flexor muscles increases after electromyostimulation training. *J Appl Physiol*. 2002;92:1383–1392.
41. Hwang SH, Lee DH, Min J, Jeon JY. Handgrip strength as a predictor of all-cause mortality in patients with chronic kidney disease undergoing dialysis: a meta-analysis of prospective cohort studies. *J Ren Nutr*. 2019;29:471–479.
42. Vogt BP, Borges MCC, Goés CR, Caramori JCT. Handgrip strength is an independent predictor of all-cause mortality in maintenance dialysis patients. *Clin Nutr*. 2016;35:1429–1433.
43. Segura-Ortí E, Martínez-Olmos FJ. Test-retest reliability and minimal detectable change scores for sit-to-stand-to-sit tests, the six-minute walk test, the one-leg heel-rise test, and handgrip strength in people undergoing hemodialysis. *Phys Ther*. 2011;91:1244–1252.
44. Isoyama N, Qureshi AR, Avesani CM, Lindholm B, Bàràny P, Heimbürger O, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. *Clin J Am Soc Nephrol*. 2014;9:1720–1728.
45. Kittiskulnam P, Chertow GM, Carrero JJ, Delgado C, Kaysen GA, Johansen KL. Sarcopenia and its individual criteria are associated, in part, with mortality among patients on hemodialysis. *Kidney Int*. 2017;92:238–247.
46. Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr*. 2006;84:475–482.
47. Fiuza-Luces C, Santos-Lozano A, Joyner M, Carrera-Bastos P, Picazo O, Zugaza JL, et al. Exercise benefits in cardiovascular disease: beyond attenuating traditional risk factors. *Nat Rev Cardiol*. 2018;15:731–743.

48. Biolo G, Pišot R, Mazzucco S, Di Girolamo FG, Situlin R, Lazzer S, et al. Anabolic resistance assessed by oral stable isotope ingestion following bed rest in young and older adult volunteers: relationships with changes in muscle mass. *Clin Nutr*. 2017;36:1420–1426.
49. Morton RW, Traylor DA, Weijs PJM, Phillips SM. Defining anabolic resistance: implications for delivery of clinical care nutrition. *Curr Opin Crit Care*. 2018;24:124–130.
50. Shad BJ, Thompson JL, Breen L. Does the muscle protein synthetic response to exercise and amino acid-based nutrition diminish with advancing age? A systematic review. *Am J Physiol Endocrinol Metab*. 2016;311:E803–E817.
51. Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA. Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. *Kidney Int*. 2003;63:291–297.
52. Parsons TL, Toffelmire EB, King-VanVlack CE. Exercise training during hemodialysis improves dialysis efficacy and physical performance. *Arch Phys Med Rehabil*. 2006;87:680–687.
53. Kong CH, Tattersall JE, Greenwood RN, Farrington K. The effect of exercise during haemodialysis on solute removal. *Nephrol Dial Transplant*. 1999;14:2927–2931.
54. Brown PDS, Rowed K, Shearer J, MacRae JM, Parker K. Impact of intradialytic exercise intensity on urea clearance in hemodialysis patients. *Appl Physiol Nutr Metab*. 2018;43:101–104.
55. Paillard T, Fréderic N, Passelergue P, Dupui P. Electrical stimulation superimposed onto voluntary muscular contraction. *Sport Med*. 2005;35:951–966.

5. Discussion

The present work shows the benefits of lifelong physical exercise for attenuating aging-induced functional decline in older adults. Moreover, exercise benefits – or those of other alternative strategies such as NMES when the former is not feasible – were also confirmed in populations at particular risk of functional decline such as in acutely hospitalized older adults and in patients with a chronic disease such as ESRD treated with hemodialysis.

Apart from the importance of these findings at the scientific level, these results are of major clinical relevance. Maintaining functional ability and particularly intrinsic capacity (i.e., the composite of all the individual's physical and mental attributes) has been proposed by the WHO as a priority to promote healthy aging. Indeed, a recent longitudinal study identified intrinsic capacity as a better predictor of functional ability (i.e., ADL function) in older adults than multimorbidity.[59] In this regard, physical exercise appears as an effective strategy for improving different components of intrinsic capacity, notably cognitive function,[60,61] psychological variables (e.g., depressive symptoms)[62] and particularly physical performance,[63–65] as confirmed in the present work. Confirming these results, a recent trial concluded that physical exercise improves intrinsic capacity in older adults aged ~73 years.[66] Moreover, a recent meta-analysis by our research group showed that exercise interventions are safe and effective in older adults for improving physical function and cognitive performance, as well as for reducing falls incidence and mortality in clinical populations.[63] Thus, physical exercise appears as an effective strategy for the improvement of intrinsic capacity and thus for the promotion of healthy aging.

Our finding of lifelong exercise as a beneficial strategy for the attenuation of aging-related physical fitness decline – as measured through VO_{2max} – is in line with a recent meta-analysis.[67] This physiological marker has proven to be a strong predictor of cardiovascular and all-cause mortality,[68–70] being indeed a better predictor than other stablished cardiovascular risk factors (e.g., hypertension, smoking).[68] In this regard,

although aging seems to be unavoidably associated with a progressive decline of VO_{2max},[71] our findings show that lifelong endurance exercise exerts a myriad of benefits (i.e., enhanced or at least preserved levels of pulmonary/cardiovascular function, blood oxygen carrying capacity, and skeletal muscle capillary density and oxidative capacity) which in turn seem to attenuate the rate of aging-related $\dot{V}O_{2max}$ decline. Thus, these data suggest that the exponential decline in $\dot{V}O_{2max}$ observed with aging might be confounded by many factors, notably the increasingly inactive lifestyle that often accompanies the aging process in the general population. Moreover, masters athletes of disciplines other than endurance (e.g., power sports) have been reported to present with a greater muscle strength than their sedentary counterparts at an advanced age (>65 years),[67] which supports the need for combining both endurance and resistance training through the lifespan. Lifelong exercise has also been reported to prevent from the aging-related degeneration in muscle properties (e.g., shifts in fiber types, reductions in capillarization and aerobic enzyme activity)[72,73] and to mediate several aspects of senescence in immune cells.[74] There is also meta-analytical evidence from longitudinal studies that regular physical exercise throughout the lifespan is associated with healthy aging.[75] Thus, lifelong exercise appears as a beneficial strategy to attenuate the multi-systemic degeneration that occurs with aging.

Apart from supporting the benefits of lifelong exercise, the present findings reinforce the need for promoting physical exercise interventions in clinical situations associated with an exacerbation of aging-related functional decline, notably hospitalization periods. As commented above, HAD affects a great proportion (approximately to one out of three) of hospitalized older adults[31] and has important consequences for the patients (including a greater risk of long-term disability, rehospitalization and mortality), their caretakers and healthcare systems.[30] In this regard, our clinical trial shows that inhospital physical

exercise programs can reduce HAD incidence by ~70%.[55] Moreover, our meta-analyis confirms that these findings are not occasional, as existing evidence shows clear benefits of inhospital exercise programs on functional ability and physical performance at both the short- and long-term (being these benefits significant even three months after discharge).[57] Therefore, the obtained results support the routine inclusion of inhospital physical exercise in healthcare systems.

In the same line, the present project shows that physical exercise can be feasible even during hemodialysis sessions, which are commonly associated with a status of complete rest. Indeed, our results show that intradialityc physical exercise improves different physical markers such as muscle strength and functional capacity. These results are clinically relevant, as hemodialysis patients present with marked functional impairments, being their physical fitness a ~50% worse than that of their healthy peers.[43] Moreover, functional capacity (which improved on average 11% in the exercise group) has been identified as a predictor of cardiovascular events, hospitalization and mortality in hemodialysis patients,[48] and lower-limb physical performance (assessed through test such as STS-10, which improved by 22% after the exercise intervention and worsened by 6% in the control group) and handgrip strength (which increased and decreased by 4%, respectively, in the exercise and control group) have also been described as predictors of mortality in this patient population.[47,76] Therefore, apart from their association with a better physical fitness, these results reinforce the implementation of physical exercise during dialysis sessions for the improvement of patients' overall health and for the reduction of morbimortality.[49]

The present project also shows that, although voluntary exercise appears as the most effective strategy for preventing disuse-induced functional decline, even patients who cannot perform voluntary exercise – such as those excessively frail or in intubated

critically ill patients – could benefit from alternative strategies such as electrostimulation or blood flow restriction.[54] Thus, the results of our meta-analysis show that the passive application of NMES can improve functional capacity and muscle strength in hemodialysis patients. These results are in accordance with previous studies that support the effectiveness of NMES for the prevention of muscle atrophy in patients with difficulties to perform voluntary exercise such as critically ill patients.[77] Therefore, NMES should be considered as an alternative strategy or as a complementary intervention to exercise for some patients.

It is important to mention that, although our findings show that physical exercise is overall beneficial for reducing functional decline, individual analyses highlight that there is some variability between subjects. Thus, although inhospital physical exercise reduced HAD incidence in older adults, 10% of the patients were considered adverse responders (that is, they suffered from HAD despite participating in the exercise program). Similarly, our study in dialysis patients shows that, although exercise led to an overall improvement of patients' physical fitness, less than 50% of the patients could be actually considered responders. It was observed in both cases that – apart from the negative influence of hospitalization length – patients with a better functional and health status at baseline (including a lower number of comorbidities) were those with a greater risk of being non-responder to exercise. Thus, it could be hypothesized that simple exercises such as those performed in acutely hospitalized older adults (i.e., walking and rising from a chair during ~20 minutes per day) or those performed with dialysis patients (i.e., strength exercises with light weights or elastic bands and aerobic exercise with a mini-bike three times per week) might not be enough to induce improvements in the fittest patients. Indeed, different studies in older adults suggest that the application of a greater training volume or intensity (for instance, through performing explosive resistance exercises) could be

more effective in participants with a better physical status. [52,78,79] Moreover, it has been reported that increasing training loads can increase the responsiveness rate in individuals initially considered as non-responders,[80,81] and indeed studies by our group have shown that increasing training intensity can induce a greater release of myokines (i.e., cytokines released by skeletal muscles) associated with beneficial cardiometabolic effects and a greater muscle anabolism.[82] It is therefore necessary to analyze whether the prescription of an individualized exercise program attending to the patients' clinical and physical characteristics (e.g., by prescribing greater training loads in those patients with a better physical status at admission) could maximize the obtained benefits.

Although our findings provide support to the role of exercise as an effective strategy for preventing aging- and disuse-induced functional decline, numerous lines of research remained to be developed. Firstly, large longitudinal studies are needed to confirm the benefits of lifelong exercise, and evidence is needed to determine if the benefits observed for endurance exercise apply to resistance one. Further evidence is also needed to determine whether certain patients' characteristics might be potentially associated with worse outcomes. For instance, current international guidelines discourage the initiation of rehabilitation programs during hospitalization for inpatients with exacerbation of chronic obstructive pulmonary disease (COPD) owing to a higher risk of long-term mortality.[83] Notwithstanding, the quality of the evidence – supported by the analysis of only three studies and with the results mostly driven by one of them[84] – was acknowledged to be 'very low'.[83] In turn, we recently reported no increase in the risk of mortality or readmission during a 12-month follow-up together with benefits on patients' functional capacity and QoL after a tailored exercise intervention in patients admitted with COPD exacerbations.[85] Finally, evidence is also needed to determine the most effective exercise interventions. For instance, although the present results support the

implementation of NMES during disuse situations, the application of NMES superimposed onto voluntary physical exercise could provide greater benefits than the latter alone in clinical populations.[86] Future research might determine the efficacy of NMES superimposed onto voluntary physical exercise for maximizing training stimuli and subsequent muscle adaptations in patients who can perform volitional exercise.

6. Conclusions

In the present project we show that lifelong physical exercise is an effective strategy for preventing the functional decline that is commonly observed with aging in older adults. Moreover, the benefits of exercise – or those of other passive strategies such as NMES -– were confirmed in older adults submitted to disuse situations such as during hospitalization periods due to an acute medical condition or during hemodialysis sessions in patients with ESRD. Our results have a marked clinical relevance, especially considering the negative consequences of functional impairments for older adults, their caretakers, and healthcare systems in general. Thus, these findings support the routine implementation of physical exercise programs in daily life and particularly in patients at risk of functional decline such as during disuse situations.

7. References

1. Sander M, Oxlund B, Jespersen A, Krasnik A, Mortensen EL, Westendorp RGJ, et al. The challenges of human population ageing. Age Ageing. 2015;44(2):185–7.

2. He W, Goodkind D, Kowal P. U.S. Census Bureau, International Population Reports. An Aging World, 2015. Washington, DC: U.S. Government Publishing Office; 2016.

3. Dodds RM, Granic A, Davies K, Kirkwood TBL, Jagger C, Sayer AA. Prevalence and incidence of sarcopenia in the very old: findings from the Newcastle 85+ Study. J Cachexia Sarcopenia Muscle. 2017;8(2):229–37.

4. Clegg A, Young J, Iliffe S, Olde Rikkert M, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62.

5. Gale CR, Cooper C, Sayer AA ihie. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. Age Ageing. 2015;44(1):162–5.

6. Bahat G, Ilhan B. Sarcopenia and the cardiometabolic syndrome: A narrative review. Eur Geriatr Med. 2016;7(3):220–3.

7. Bone AE, Hepgul N, Kon S, Maddocks M. Sarcopenia and frailty in chronic respiratory disease: Lessons from gerontology. Chron Respir Dis. 2017;14(1):85–99.

8. Landi F, Cruz-Jentoft AJ, Liperoti R, Russo A, Giovannini S, Tosato M, et al. Sarcopenia and mortality risk in frail olderpersons aged 80 years and older: Results from iLSIRENTE study. Age Ageing. 2013;42(2):203–9.

9. Mijnarends D, Luiking Y, Halfens R, Evers S, Lenaerts E, Verlaan S, et al. Muscle, Health and Costs: A Glance at their Relationship. J Nutr Heal Aging. 2018;22(7):766–73.

10. Steffl M, Sima J, Shiells K, Holmerova I. The increase in health care costs associated with muscle weakness in older people without long- term illnesses in the Czech republic: results from the survey of health, Ageing and retirement in europe (SHARE). Clin Interv Aging. 2017;12:2003–7.

11. Beard JR, Officer A, De Carvalho IA, Sadana R, Pot AM, Michel JP, et al. The World report on ageing and health: A policy framework for healthy ageing. Lancet. 2016;387(10033):2145–54.

12. Joyner MJ, Coyle EF. Endurance exercise performance: the physiology of champions. J Physiol. 2008;586(1):35–44.

13. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement from the American Heart Association. Circulation. 2016;134(24):e653–99.

14. Lazarus NR, Izquierdo M, Higginson IJ, Harridge. SDR. Exercise Deficiency Diseases of Ageing: The Primacy of Exercise and Muscle Strengthening as First Line Therapeutic Agents to Combat Frailty. J Am Med Dir Assoc. 2018;19(9):741–3.

15. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. Lancet Glob Heal. 2018;6(10):E1077–86.

16. Noakes T, Spedding M. Olympics: Run for your life. Nature. 2012;487(7407):295–6.

17. Harridge SDR, Lazarus NR. Physical Activity, Aging, and Physiological Function.

Physiology. 2017;32(2):152–61.

18. Tanaka H, Seals DR. Dynamic exercise performance in Masters athletes: insight into the effects of primary human aging on physiological functional capacity. J Appl Physiol. 2003;95(5):2152–62.

19. Lazarus NR, Harridge SDR. Declining performance of master athletes: silhouettes of the trajectory of healthy human ageing? J Physiol. 2017;595(9):2941–8.

20. Lepers R, Stapley PJ. Master athletes are extending the limits of human endurance. Front Physiol. 2016;7(DEC):1–8.

21. Bell KE, von Allmen MT, Devries MC, Phillips SM. Muscle Disuse as a Pivotal Problem in Sarcopenia-related Muscle Loss and Dysfunction. J Frailty Aging. 2016;5(1):33–41.

22. Pavon JM, Sloane RJ, Pieper CF, Colón-Emeric CS, Cohen HJ, Gallagher D, et al. Accelerometer-Measured Hospital Physical Activity and Hospital-Acquired Disability in Older Adults. J Am Geriatr Soc. 2020;68(2):261–5.

23. Zisberg A, Shadmi E, Sinoff G, Gur-Yaish N, Srulovici E, Admi H. Low mobility during hospitalization and functional decline in older adults. J Am Geriatr Soc. 2011;59(2):266–73.

24. Agmon M, Zisberg A, Gil E, Rand D, Gur-Yaish N, Azriel M. Association between 900 steps a day and functional decline in older hospitalized patients. JAMA Intern Med. 2017;177(2):272–4.

25. Brown CJ, Redden DT, Flood KL, Allman RM. The underrecognized epidemic of low mobility during hospitalization of older adults. J Am Geriatr Soc. 2009;57(9):1660–5.

26. Callen BL, Mahoney JE, Grieves CB, Wells TJ, Enloe M. Frequency of hallway ambulation by hospitalized older adults on medical units of an academic hospital. Geriatr Nurs (Minneap). 2004;25(4):212–7.

27. Coker RH, Hays NP, Williams RH, Wolfe RR, Evans WJ. Bed rest promotes reductions in walking speed, functional parameters, and aerobic fitness in older, healthy adults. Journals Gerontol - Ser A Biol Sci Med Sci. 2015;70(1):91–6.

28. Dirks ML, Wall BT, Nilwik R, Weerts DHJM, Verdijk LB, van Loon LJC. Skeletal muscle disuse atrophy is not attenuated by dietary protein supplementation in healthy older men. J Nutr. 2014;144(8):1196–203.

29. Tanner RE, Brunker LB, Agergaard J, Barrows KM, Briggs RA, Kwon OS, et al. Age-related differences in lean mass, protein synthesis and skeletal muscle markers of proteolysis after bed rest and exercise rehabilitation. J Physiol. 2015;593(18):4259–73.

30. Covinsky KE, Pierluissi E, Story THEPS. Hospitalization-Associated Disability "She Was Probably Able to Ambulate, but I'm Not Sure." JAMA. 2011;306(16):1782–93.

31. Loyd C, Markland AD, Zhang Y, Fowler M, Harper S, Wright NC, et al. Prevalence of Hospital-Associated Disability in Older Adults: A Meta-analysis. J Am Med Dir Assoc. 2020;21(4):455–61.

32. Boyd C, Landefeld C, Counsell S, Palmer R, Fortinsky R, Kresevic D, et al. Recovery in Activities of Daily Living Among Older Adults Following Hospitalization for Acute Medical Illness. J Am Geriatr Soc. 2008;56(12):2171–9.

33. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J.

Importance of functional measures in predicting mortality among older hospitalized patients. JAMA. 1998;279(15):1187–98.

34. Fortinsky RH, Covinsky KE, Palmer RM, Landefeld CS. Effects of functional status changes before and during hospitalization on nursing home admission of older adults. Journals Gerontol - Ser A Biol Sci Med Sci. 1999;54(10):521–6.

35. Wall BT, Snijders T, Senden JMG, Ottenbros CLP, Gijsen AP, Verdijk LB, et al. Disuse impairs the muscle protein synthetic response to protein ingestion in healthy men. J Clin Endocrinol Metab. 2013;98(12):4872–81.

36. Dirks ML, Wall BT, Van De Valk B, Holloway TM, Holloway GP, Chabowski A, et al. One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. Diabetes. 2016;65(10):2862–75.

37. McGlory C, von Allmen MT, Stokes T, Morton RW, Hector AJ, Lago BA, et al. Failed Recovery of Glycemic Control and Myofibrillar Protein Synthesis With 2 wk of Physical Inactivity in Overweight, Prediabetic Older Adults. Journals Gerontol Ser A. 2017;00(00):1–8.

38. Biensø RS, Ringholm S, Kiilerich K, Aachmann-Andersen NJ, Krogh-Madsen R, Guerra B, et al. GLUT4 and glycogen synthase are key players in bed rest-induced insulin resistance. Diabetes. 2012;61(5):1090–9.

39. Ehlenbach WJ, Crane PK, Haneuse SJPA, Carson SS, Curtis JR, Larson EB. Association Between Acute Care and Critical Illness Hospitalization. JAMA. 2010;303(8):763–70.

40. Szczech LA, Lazar IL. Projecting the United States ESRD population: issues

regarding treatment of patients with ESRD. Kidney Int Suppl. 2004;66(90):S3–7.

41. McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD incidence and prevalence in the United States through 2030. J Am Soc Nephrol. 2019;30(1):127–35.

42. Leal VO, Stockler-Pinto MB, Farage NE, Aranha LN, Fouque D, Anjos LA, et al. Handgrip strength and its dialysis determinants in hemodialysis patients. Nutrition. 2011;27(11–12):1125–9.

43. Painter P. Physical functioning in end-stage renal disease patients: update 2005. Hemodial Int. 2005;9(3):218–35.

44. O'Hare AM, Tawney K, Bacchetti P, Johansen KL. Decreased survival among sedentary patients undergoing dialysis: Results from the dialysis morbidity and mortality study wave 2. Am J Kidney Dis. 2003;41(2):447–54.

45. Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. Kidney Int. 2004;65(2):719–24.

46. Stack AG, Molony DA, Rives T, Tyson J, Murthy BVR. Association of physical activity with mortality in the US dialysis population. Am J Kidney Dis. 2005;45(4):690–701.

47. Roshanravan B, Robinson-Cohen C, Patel K V., Ayers E, Littman AJ, de Boer IH, et al. Association between Physical Performance and All-Cause Mortality in CKD. J Am Soc Nephrol. 2013;24(5):822–30.

48. Torino C, Manfredini F, Bolignano D, Aucella F, Baggetta R, Barillà A, et al. Physical Performance and Clinical Outcomes in Dialysis Patients: A Secondary

Analysis of the Excite Trial. Kidney Blood Press Res. 2014;39(2–3):205–11.

49. Morishita S, Tsubaki A, Shirai N. Physical function was related to mortality in patients with chronic kidney disease and dialysis. Hemodial Int. 2017;21(4):483–9.

50. Majchrzak KM, Pupim LB, Chen K, Martin CJ, Gaffney S, Greene JH, et al. Physical activity patterns in chronic hemodialysis patients: comparison of dialysis and nondialysis days. J Ren Nutr. 2005;15(2):217–24.

51. Johansen KL, Chertow GM, Kutner NG, Dalrymple LS, Grimes BA, Kaysen GA. Low level of self-reported physical activity in ambulatory patients new to dialysis. Kidney Int. 2010;78(11):1164–70.

52. Valenzuela P, Castillo-García A, Morales J, Izquierdo M, Serra-Rexach J, Santos-Lozano A, et al. Physical exercise in the oldest old. Compr Physiol. 2019;9(4):1281–304.

53. Valenzuela PL, Maffiuletti NA, Joyner MJ, Lucia A, Lepers R. Lifelong Endurance Exercise as a Countermeasure Against Age-Related VO2max Decline: Physiological Overview and Insights from Masters Athletes. Sport Med. 2020;50(4):703–16.

54. Valenzuela PL, Morales JS, Pareja-Galeano H, Izquierdo M, Emanuele E, de la Villa P, et al. Physical strategies to prevent disuse-induced functional decline in the elderly. Ageing Res Rev. 2018;47(July):80–8.

55. Ortiz-Alonso J, Bustamante-Ara N, Valenzuela PL, Vidán M, Rodríguez-Romo G, Mayordomo-Cava J, et al. Effect of a simple exercise programme on hospitalisation-associated disability in older patients: a randomised controlled trial.

JAMDA. 2020;21(4):531–7.

56. Valenzuela PL, Ortiz-alonso J, Bustamante-ara N, Vid T, Hidalgo-gamarra M, Myriel L, et al. Individual Responsiveness to Physical Exercise Intervention in Acutely Hospitalized Older Adults. J Clin Med. 2020;9(3):797.

57. Valenzuela P, Morales J, Castillo-García A, Mayordomo-Cava J, García-Hermoso A, Izquierdo M, et al. Effects of exercise interventions on the functional status of acutely hospitalised older adults: A systematic review and meta-analysis. Ageing Res Rev. 2020;61:101076.

58. Valenzuela PL, de Alba A, Pedrero-Chamizo R, Morales JS, Cobo F, Botella A, et al. Intradialytic exercise: One size doesn't fit all. Front Physiol. 2018;9(JUL):844.

59. Beard JR, Jotheeswaran AT, Cesari M, Araujo De Carvalho I. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. BMJ Open. 2019;9(11):e026119.

60. Valenzuela PL, Castillo-García A, Morales JS, de la Villa P, Hampel H, Emanuele E, et al. Exercise benefits on Alzheimer's disease: State-of-the-science. Ageing Res Rev. 2020;62(May):101108.

61. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: A systematic review with meta-Analysis. Br J Sports Med. 2018;52(3):154–60.

62. Barbour KA, Blumenthal JA. Exercise training and depression in older adults. Neurobiol Aging. 2005;26(SUPPL.):119–23.

63. García-Hermoso A, Ramirez-Vélez R, Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, Valenzuela PL, et al. Safety and Effectiveness of Long-Term

Exercise Interventions in Older Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Sport Med. 2020;50(6):1095–106.

64. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, Sitjà-Rabert M, Salvà A. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: A systematic review and meta-analysis. Arch Phys Med Rehabil. 2014;95(4).

65. Bao W, Sun Y, Zhang T, Zou L, Wu X, Wang D, et al. Exercise Programs for Muscle Mass, Muscle Strength and Physical Performance in Older Adults with Sarcopenia: A Systematic Review and Meta-Analysis. Aging Dis. 2020;11(4):863.

66. Huang CH, Umegaki H, Makino T, Uemura K, Hayashi T, Kitada T, et al. Effect of Various Exercises on Intrinsic Capacity in Older Adults With Subjective Cognitive Concerns. J Am Med Dir Assoc. 2020;S1525-8610(65):30570–3.

67. Mckendry J, Breen L, Shad BJ, Greig CA. Muscle morphology and performance in master athletes: A systematic review and meta-analyses. Ageing Res Rev. 2018;45(January):62–82.

68. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood J. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793–801.

69. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treadmill Testing. JAMA Netw Open. 2018;1(6):e183605.

70. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular

Events. J Am Med Assoc. 2009;301(19):2024–35.

71. Astrand I, Astrand P, Hallback I, Kilbom A. Reduction in maximal oxygen uptake with age. J Appl Physiol. 1973;35(5):649–54.

72. Pollock RD, O'Brien KA, Daniels LJ, Nielsen KB, Rowlerson A, Duggal NA, et al. Properties of the vastus lateralis muscle in relation to age and physiological function in master cyclists aged 55–79 years. Aging Cell. 2018;17(2).

73. Gries KJ, Raue U, Perkins RK, Lavin KM, Overstreet BS, D'Acquisto LJ, et al. Cardiovascular and skeletal muscle health with lifelong exercise. J Appl Physiol. 2018;125(5):1636–45.

74. Duggal NA, Pollock RD, Lazarus NR, Harridge S, Lord JM. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. Aging Cell. 2018;17(2).

75. Daskalopoulou C, Stubbs B, Kralj C, Koukounari A, Prince M, Prina AM. Physical activity and healthy ageing: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2017;38:6–17.

76. Leal VO, Mafra D, Fouque D, Anjos LA. Use of handgrip strength in the assessment of the muscle function of chronic kidney disease patients on dialysis: A systematic review. Nephrol Dial Transplant. 2011;26(4):1354–60.

77. Maffiuletti NA, Roig M, Karatzanos E, Nanas S. Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: A systematic review. BMC Med. 2013;11(1):1.

78. Straight CR, Lindheimer JB, Brady AO, Dishman RK, Evans EM. Effects of Resistance Training on Lower-Extremity Muscle Power in Middle-Aged and Older

Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Sport Med. 2016;46(3):353–64.

79. Tschopp M, Sattelmayer MK, Hilfiker R. Is power training or conventional resistance training better for function in elderly persons? A meta-analysis. Age Ageing. 2011;40(5):549–56.

80. Montero D, Lundby C. Refuting the myth of non-response to exercise training: 'non-responders' do respond to higher dose of training. J Physiol. 2017;595(11):3377–87.

81. Ross R, de Lannoy L, Stotz PJ. Separate Effects of Intensity and Amount of Exercise on Interindividual Cardiorespiratory Fitness Response. Mayo Clin Proc. 2015;90(11):1506–14.

82. He Z, Tian Y, Valenzuela PL, Huang C, Zhao J, Hong P, et al. Myokine/adipokine response to "aerobic" exercise: Is it just a matter of exercise load? Front Physiol. 2019;10(MAY):1–9.

83. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PMA, Albert RK, Anzueto A, et al. Management of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017 Oct;50(4).

84. Greening NJ, Williams JEA, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: Randomised controlled trial. BMJ. 2014 Jul;349:g4315.

85. Martínez-Velilla N, Valenzuela PL, Zambom-Ferraresi F, Sáez de Asteasu ML, Ramírez-Vélez R, García-Hermoso A, et al. Tailored exercise is safe and beneficial

for acutely hospitalised older adults with chronic obstructive pulmonary disease. Eur Respir J. 2020;2001048.

86. Paillard T, Fréderic N, Passelergue P, Dupui P. Electrical Stimulation superimposed onto Voluntary Muscular Contraction. Sport Med. 2005;35(11):951–66.

8. Appendices

Other related articles published during this doctoral thesis

- **Valenzuela PL**, Morales JS, Santos-Lozano A, Serra-Rexach JA, Izquierdo M, Lucia A (2018) mHealth and Aging. JAMDA. 19(9):810-811. IF (2018): 4.899. Q1 (6/53).

- **Valenzuela PL**, Morales JS, Santos-Lozano A, Lucia A (2018) Centenarians breaking records: nature or nurture? Age and Ageing. 47(5):761-662. IF (2018): 4.511. Q1 (9/53).

- **Valenzuela PL**, Morales JS, Emanuele E, Pareja-Galeano H, Lucia A (2019) Supplements with purported effects on muscle mass and strength. Eur J Nutr. 58 (8): 2983-3008. IF (2019): 4.664. Q1 (16/89).

- **Valenzuela PL**, Cobo F, Diez-Vega I, Sánchez-Hernández R, Pedrero-Chamizo R, Verde-Rollo Z, González-Gross M, Santiago C, Pérez Ruiz M (2019) Physical performance, plasma S-klotho, and all-cause mortality in elderly dialysis patients: A prospective cohort study. Experimental gerontology. 122:123-128. IF (2019): 3.376. Q2 (19/51).

- **Valenzuela PL**, Santos-Lozano A, Lucia A (2019) More on the Record-Breaking Performance in a 70-Year-Old Marathoner. New England Journal of Medicine. 381 (3): 293-294. IF (2018): 74.699. Q1 (1/165).

- **Valenzuela PL**, Morales JS, Fiuza-Luces C, de la Villa P, Santos-Lozano A, Lucia A (2019) Preventing Alzheimer's disease: why not targeting the muscle first? JAMDA. 20 (1), 101-102. IF (2019): 4.367. Q1 (8/51).

- **Valenzuela PL**, Maffiuletti NA, Lucia A, Lepers R (2019) The sub 6-h project. Age and Ageing. 48 (6): 928-929. IF (2019): 4.902. Q1 (6/51).

- Martinez-Velilla N, **Valenzuela PL**, Zambom-Ferraresi F, Sáez de Asteasu M, Ramirez-Vélez R, García-Hermoso A, Lucia A, Izquierdo M (2020) Tailored exercise is

safe and beneficial for acutely hospitalized older adults with chronic obstructive pulmonary disease. European Respiratory Journal. In press. IF (2019): 12.339. Q1 (4/64).

- **Valenzuela PL**, Castillo-García A, Morales JS, Lista S, de la Villa P, Emanuele E, Hampel H, Lucia A (2020) Exercise benefits on Alzheimer's disease: state-of-the-science. Ageing Research Reviews. 62: 101108. IF (2019): 10.616. Q1 (1/51).

- Santos-Lozano A, **Valenzuela PL**, Llavero F, Lista S, Carrera-Bastos P, Hampel H, Pareja-Galeano H, Gálvez BG, López JA, Vázquez J, Emanuele E, Zugaza JL, Lucia A (2020) Successful aging: insights from proteome analyses of healthy centenarians. Aging. 12 (4): 3502-3515. IF (2019): 4.831. Q1 (7/51).

- García-Hermoso A, Ramirez-Velez R, Sáez de Asteasu ML, Martinez-Velilla N, Zambom-Ferraresi F, **Valenzuela PL**, Lucia A, Izquierdo M (2020) Safety and Effectiveness of Long-Term Exercise Interventions in Older Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Sports Med. 50 (6): 1095-1106. IF (2019): 8.551. Q1 (2/85).

- **Valenzuela PL**, Santos-Lozano A, Lista S, Serra-Rexach JA, Emanuele E, Lucia A (2020) Coronavirus lockdown: forced inactivity for the oldest old? JAMDA. S1525-8610(20)30285-1. IF (2019): 4.367. Q1 (8/51).

- **Valenzuela PL**, Joyner MJ, Lucia A (2020) Early mobilization in hospitalized patients with COVID-19. Ann Phys Rehabil Med. 63 (4):384-385. IF (2019): 3.657. Q1 (4/68).

- **Valenzuela PL**, Maffiuletti NA, Sane H, Schütz N, Rudin B, Nef T, Urwyler P (2020) Isometric strength measures are superior to the timed up and go test for fall prediction in older adults: Results from a prospective cohort study. Clinical Interventions in Aging. In press. IF (2019): 3.023. Q2 (21/51).

- **Valenzuela PL**, Maffiuletti NA, Tringali G, de Col A, Sartorio A (2020) Obesity-associated poor muscle quality: prevalence and association with age, sex, and body mass index. BMC musculoskeletal disorders. In press. IF (2019): 1.879. Q3 (44/82).

- Martinez-Velilla N, **Valenzuela PL**, Sáez de Asteasu M, Zambom-Ferraresi F, Ramirez-Vélez R, García-Hermoso A, Librero-López J, Gorricho J, Esparza Pérez F, Lucia A, Izquierdo M (2020) Effects of a tailored exercise intervention in acutely hospitalized diabetic oldest old adults: an ancillary analysis. The Journal of Clinical Endocrinology & Metabolism. In press. IF (2019): 5.399. Q1 (21/143).

DOCTORAL PROGRAM IN HEALTH SCIENCES

Aging- and muscle disuse-induced functional decline: physiological mechanisms and preventive strategies

PEDRO L. VALENZUELA TALLÓN 2020