Exercise Attenuates the Major Hallmarks of Aging

Nuria Garatachea,1–3,* Helios Pareja-Galeano,2,4,* Fabian Sanchis-Gomar,2 Alejandro Santos-Lozano,2 Carmen Fiuza-Luces,2,4 María Morán,2,5 Enzo Emanuele,6 Michael J. Joyner,7,* and Alejandro Lucia2,4,*

Abstract

Regular exercise has multi-system anti-aging effects. Here we summarize how exercise impacts the major hallmarks of aging. We propose that, besides searching for novel pharmaceutical targets of the aging process, more research efforts should be devoted to gaining insights into the molecular mediators of the benefits of exercise and to implement effective exercise interventions for elderly people.

Introduction

The number of people aged ≥ 60 years worldwide is expected to nearly triple by 2050, with the “oldest old” group (≥ 85 years) being the most rapidly expanding segment. A growing challenge is to maintain elderly people independently until end of life. In them, functional independence is directly dependent on physical fitness, i.e. “the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy [leisure] pursuits and to meet unforeseen emergencies.”1 In turn, physical fitness is determined by several measurable health-related phenotypes, including mainly cardiorespiratory fitness and muscle function.1 Among the physiological changes associated with aging, those affecting the cardiorespiratory and vascular system and skeletal muscles most affect physical fitness, whereas exercise can attenuate multi-system age declines, as explained below.

Summary of the Impact of Aging on the Main Physical Fitness—Related Phenotypes

Aging and cardiorespiratory fitness

Maximal oxygen uptake (VO_{2}\text{max}; sometimes referred to as maximal aerobic capacity or simply aerobic capacity or aerobic endurance) is a main indicator of cardiorespiratory fitness. There is variability among studies,2–4 but the average rate of VO_{2}\text{max} decline in old people is ≥ 4–5 mL·kg^{-1}·min^{-1}/decade.5 Mostly reduced maximal cardiac output6–10 but also a decline in maximal arteriovenous oxygen difference (a-vO_{2} \text{diff}) (minus ~ 3%/decade)7,11 contribute to age reductions in VO_{2}\text{max}.12,13 Aging skeletal muscles have a low capacity to use O_{2} due to several factors, such as decreased muscle mass14,15, increased peripheral resistance16, reduced muscle capillary density,17 endothelial dysfunction,18 changes in skeletal muscle microcirculation,19 and reduced muscle oxidative capacity.20

Aging and muscle function

Muscle mass usually starts to decline after 25–30 years of age,21,22 such that on average 40% of muscle mass is lost by 80 years.22,23 In turn, a quantitative loss in muscle cross-sectional area is a major contributor to the decrease in muscle strength seen with advancing age, i.e., after 60–70 years of age.24 The term “sarcopenia” was originally created to refer to age-related loss of muscle mass with consequent loss of strength.25 There are now four international definitions of sarcopenia.26–29 In essence they all agree, requiring a measure of impaired walking capability (either low gait speed or a limited endurance [distance] in a 6-min walk), together with an appendicular lean mass of less than 2 standard deviations of a sex- and ethnically-corrected normal level for individuals 20–30 years old. Sarcopenia (see below for details on signaling pathways involved) occurs due

1Faculty of Health and Sport Science, University of Zaragoza, Huesca, Spain.
2Mitochondrial and Neuromuscular Diseases Laboratory, Hospital Universitario 12 de Octubre, Research Institute (i + 12), Madrid, Spain.
3GENUD (Growth, Exercise, Nutrition and Development) Research Group, University of Zaragoza, Zaragoza, Spain.
4European University of Madrid, Madrid, Spain.
5CIBER de Enfermedades Raras, U723, Madrid, Spain.
6Department of Health Sciences, University of Pavia, Pavia, Italy.
7Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota.
*These authors equally contributed to this work.
*Shared senior authorship.

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to several age-related factors, such as gradual muscle denervation,\textsuperscript{23,30} diminished satellite cells,\textsuperscript{31} low muscle protein synthesis,\textsuperscript{32} low anabolic hormone levels,\textsuperscript{33} malnutrition,\textsuperscript{34} increased pro-inflammatory cytokines,\textsuperscript{35} oxidative stress,\textsuperscript{36} mitochondrial dysfunction,\textsuperscript{37–40} and physical inactivity.\textsuperscript{41} Although there are differences between studies, on average, 5%–13% and 11%–50% of people aged 60–70 years and ≥ 80 years, respectively, suffer sarcopenia,\textsuperscript{42–47} with a higher prevalence (68%) reported in nursing home residents ≥ 70 years.\textsuperscript{48} Sarcopenia needs to be differentiated from ``cachexia,''' a combination of both muscle and fat loss that is usually attributable to an excess of catabolic cytokines associated with a disease process, e.g., cancer.\textsuperscript{39–51} Sarcopenia is linked with increased disability, falls, hospitalization, nursing home admission, and mortality.\textsuperscript{48,52–54}

Frailty and disability

A consequence of the aforementioned effects of aging on cardiorespiratory and muscle fitness (especially sarcopenia), alone or in combination with co-morbidities such as neurodegeneration, is the “frailty syndrome.”\textsuperscript{55} Although no single operational definition of the frailty syndrome has been agreed upon, two major definitions with proposed as-assessment tools have predominated over the past decade—the frailty phenotype, also known as Fried’s definition,\textsuperscript{56} and the frailty index.\textsuperscript{57} The most widely cited is the frailty phenotype, which is operationalized as a syndrome meeting three or more of the following five phenotypic criteria: Weakness as measured by low grip strength, slowness (low walking speed), low level of physical activity, low energy or self-reported exhaustion, and unintentional weight loss.\textsuperscript{56} A prefrail stage, in which one or two criteria are present, identifies a subset at high risk of progressing to frailty. Older individuals with none of the above five criteria are classified as nonfrail. The frailty index was developed on the basis of a comprehensive geriatric assessment by counting the number of deficits accumulated, including diseases, physical and cognitive impairments, psychosocial risk factors, and common geriatric syndromes other than frailty.\textsuperscript{57,58} Whereas the frailty index may have clinical utility in risk assessment and stratification, it is less clear that it adds significant value to comprehensive geriatric assessment.\textsuperscript{59}

Frailty is an important and growing problem in aging western populations, because it potentially affects 20%–30% of adults older than 75 years.\textsuperscript{60} For instance, the prevalence of prefrail and frail individuals is high in the Spanish population (41.8% and 8.4%, respectively) and increases with age, according to a recent a population-based study conducted on 2488 individuals aged 65 years and older in a central area of the country.\textsuperscript{61} On the other hand, frailty could eventually result in disability,\textsuperscript{62} i.e., “difficulty or dependency in carrying out activities necessary for independent living, including roles, tasks needed for self-care and household chores, and other activities important for a person’s quality of life.”\textsuperscript{63} For the above-mentioned reasons, it is of paramount medical importance to attenuate age-related declines in physical fitness. Yet no single drug can reverse the age-related loss of physical fitness because none benefits all of the systems involved, whereas regular exercise has multi-system anti-aging effects (see below and Fig. 1, left column for a summary).

Exercise Attenuates Fitness and Multisystem Age-Related Declines

Benefits of exercise (particularly aerobic exercise) in cardiorespiratory fitness/cardiovascular disease

Regular exercise, particularly dynamic exercise of moderate intensity (≤ 70% of VO\textsubscript{2}max or ≤ 80% of maximum heart rate) involving mostly the aerobic energy pathway and large muscle mass (e.g., brisk walking, bicycling) attenuates age declines in cardiorespiratory fitness (see Chodzko-Zajko et al.\textsuperscript{64} for an in-depth review and experts’ recommendations). This type of exercise, commonly referred to as “aerobic exercise” (or “endurance exercise”), has a restoring effect on an important risk factor of cardiovascular disease (CVD), i.e., endothelial dysfunction.\textsuperscript{65–67} It also increases endothelial nitric oxide (NO\textsubscript{•}) production and thus vascular tone regulation. Regular bouts of exercise-increased laminar flow activate (through phosphorylation via protein kinase B, Akt) endothelial NO\textsubscript{•} synthase while attenuating NO\textsubscript{•} degradation into reactive oxygen species (ROS) and reactive nitrogen species.\textsuperscript{68} Together with increased angiogenesis (see further below), an additional benefit of aerobic exercise in endothelial health is stimulation of macrophage-mediated reverse cholesterol transport through activation of peroxisome proliferator-activated receptor gamma (PPAR\gamma).\textsuperscript{69,70} Yet aging autonomic dysfunction has a synergistic effect together with endothelial dysfunction in increasing CVD risk\textsuperscript{71} and raises the risk of a leading cause of death in most industrialized countries, sudden death due to ventricular fibrillation.\textsuperscript{72}

During aging, the sympathetic nervous system (SNS) outflow to several peripheral tissues increases to stimulate thermogenesis and thus to prevent increasing adiposity.\textsuperscript{73} Chronically activated SNS has deleterious effects on the cardiovascular system, i.e., reduced leg blood flow, increased arterial blood pressure, impaired baroreflex function and hypertrophy of large arteries; it can also increase insulin resistance, thereby raising the risk of metabolic syndrome.\textsuperscript{74,75} Importantly, aerobic exercise training (e.g., brisk walking) has a beneficial, dose-response effect in attenuating aging autonomic system dysfunction, with trained elderly individuals showing similar baroreflex function compared with their moderately active younger peers.\textsuperscript{76} Heart rate variability (HRV), a marker of autonomic function and a powerful predictor of CVD outcome (high HRV is associated with a better prognosis), increases with aerobic exercise training in old people.\textsuperscript{77} Reduced angiotensin II, increased NO\textsubscript{•}, and mainly improved vagal modulation and decreased sympathetic tone are implicated in the beneficial exercise effects on HRV.\textsuperscript{78}

Benefits of exercise (particularly resistance exercise) in the aging muscle function

Training programs, especially if including resistance (strength) exercises (i.e., movements, such as weightlifting or exercises with resistance bands, performed against a specific external force that is regularly increased during training) are especially useful for improving muscle mass and/or strength in the elderly,\textsuperscript{79} including in the oldest old\textsuperscript{80} (see Table 1 for a summary of controlled exercise interventions [mostly based on resistance exercises] in the oldest
In general, published resistance exercise interventions in old people had a duration ranging from 4 to 48 weeks and were in agreement with accepted or "traditional" exercise recommendations for older people, with the usual weekly schedule including two to three nonconsecutive sessions with one to three sets of 10–15 repetitions of classic weightlifting exercises, such as leg presses.

Other interventions feasible in old people include "high-velocity resistance training," i.e., focusing on speed of movement, or even explosive-type heavy-resistance training, e.g., weightlifting exercises with a load equivalent to 75%–80% of one repetition maximum (1RM) and performed with maximal intentional acceleration of the training load during the concentric movement phase. In general, besides being feasible and well tolerated even by the oldest old, this alternative type of intervention would elicit similar or even higher improvements in functional performance and disability compared with more traditional, lower-velocity resistance training. Another approach is the use of a weighted vest, which has proved effective to improve perceived health in old people, as well as lateral stability, lower-body muscular strength, muscular power,
Table 1. Summary of Controlled Exercise Interventions (Mostly Based on Resistance Exercises) in the Oldest Old

<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th>n (% women)</th>
<th>Mean age (SD or range in years)</th>
<th>Length (weeks)</th>
<th>Type</th>
<th>Frequency (sessions/week)</th>
<th>Exercises/session (repetitions per × exercise)</th>
<th>Intensity/duration</th>
<th>Effects</th>
</tr>
</thead>
</table>
| 356       | Exercise| 46 (72%)    | 80 (7)                          | 24             | Low intensities+ | 3                        | Flexibility, balance, coordination, movement speed and strength of all major muscle groups | 5–15 min (0–12 weeks) | † Knee extension strength  
|           |         |             |                                 |                |            |                          |                                               |                   | † Fast walking speed  
|           |         |             |                                 |                |            |                          |                                               |                   | † Total free mass |
| Control   | 44 (77%)| 81 (8)      | 24                              |                | 3          |                        | Flexibility, balance, coordination, movement speed and strength of all major muscle groups |                   | † Knee extension strength  
|           |         |             |                                 |                |            |                          |                                               |                   | † Fast walking speed  
|           |         |             |                                 |                |            |                          |                                               |                   | † Total free mass |
|           |         |             |                                 |                |            |                          |                                               |                   | (Significantly less pronounced than in the exercise group) |
| 357       | Exercise| 11 (91%)    | 88.6 (86–95)                    | 12             | Strength    | 3                        | 8      8x 90° knee flexion  
|           |         |             |                                 |                |            |                          |                                               |                   | † Extensor and flexor muscle strength |
| Control   | 12 (92%)| 90.6 (86–95)| 12                              |                | No PA       | 2                        | 8      8x 90° knee flexion  
|           |         |             |                                 |                |            |                          |                                               |                   | † Extensor and flexor muscle strength (Significantly less pronounced than in the exercise group) |
| 358       | Exercise| 11 (NA)     | 93.4 (3.2)                     | 12             | Strength +  | 2                        | 8–10x upper body  
|           |         |             |                                 |                |            |                          |                                               |                   | † Quadriceps femoris CSA  
|           |         |             |                                 |                |            |                          |                                               |                   | † Hand grip  
|           |         |             |                                 |                |            |                          |                                               |                   | † Hip flexion strength  
|           |         |             |                                 |                |            |                          |                                               |                   | † Knee extension strength  
|           |         |             |                                 |                |            |                          |                                               |                   | † Upper-body 1RM  
|           |         |             |                                 |                |            |                          |                                               |                   | † Lower-body 1RM  
|           |         |             |                                 |                |            |                          |                                               |                   | † Maximal power at 30% 1RM  
|           |         |             |                                 |                |            |                          |                                               |                   | † Maximal power at 60% 1RM  
|           |         |             |                                 |                |            |                          |                                               |                   | † Falls incidence  
|           |         |             |                                 |                |            |                          |                                               |                   | = Quadriceps femoris CSA  
|           |         |             |                                 |                |            |                          |                                               |                   | † Hand grip strength  
|           |         |             |                                 |                |            |                          |                                               |                   | † Hip flexion strength  
|           |         |             |                                 |                |            |                          |                                               |                   | † Knee extension strength  
| Control   | 13 (NA) | 90.1 (1.1)  | 12                              |                | Mobility    | 4                        | Active and passive movements | 30 min            |                                                                  |

(continued)
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<th>Group</th>
<th>n (% women)</th>
<th>Mean age (SD or range in years)</th>
<th>Length (weeks)</th>
<th>Type</th>
<th>Frequency (sessions/week)</th>
<th>Sets</th>
<th>Exercises/session (repetitions per (×) exercise)</th>
<th>Intensity/duration</th>
<th>Effects</th>
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<tbody>
<tr>
<td>359</td>
<td>Exercise</td>
<td>107 (55%)</td>
<td>82.8 (4.48)</td>
<td>48</td>
<td>Functional exercise</td>
<td>Several</td>
<td>Set of exercise</td>
<td>Ankle strength, knee strength and function effects were significantly better than in control group</td>
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<td>360</td>
<td>Exercise</td>
<td>15 (NA)</td>
<td>86.7 (6.1) (77–98)</td>
<td>10</td>
<td>Warm-up + Strength + Balance</td>
<td>3</td>
<td>10–15 × muscle group</td>
<td>10 min</td>
<td>Elastic therabands and soft weights</td>
<td>Muscle-strength</td>
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<tr>
<td>361</td>
<td>Exercise + Nutritional supplement</td>
<td>25 (64%)</td>
<td>86.2 (1.0) (72–95)</td>
<td>10</td>
<td>Strength</td>
<td>3</td>
<td>8 × hip extensor</td>
<td>80% 1RM</td>
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<tr>
<td>361</td>
<td>Nutritional supplement + Placebo activities</td>
<td>24 (71%)</td>
<td>85.7(1.2) (75–97)</td>
<td>10</td>
<td>240 mL liquid + CHO (60%) + fat (23%) + soy-based protein (17%) Aerobic or flexibility activities</td>
<td>3</td>
<td>3 activities (e.g., walking)</td>
<td>No effect</td>
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<tr>
<td>361</td>
<td>Placebo activities + Placebo supplement</td>
<td>26 (54%)</td>
<td>89.2 (0.8) (78–98)</td>
<td>10</td>
<td>Aerobic or flexibility activities Minimally nutritive (4 kcal)</td>
<td>3</td>
<td>3 activities (e.g., walking)</td>
<td>No effect</td>
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<th>Sets</th>
<th>Exercises/session (repetitions per exercise)</th>
<th>Intensity/duration</th>
<th>Effects</th>
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<tr>
<td>362 Exercise + Traditional balance training</td>
<td>12 (50%)</td>
<td>81.1 (6.0) (69–95)</td>
<td>12</td>
<td>Strength +</td>
<td>2</td>
<td>Larger over extremity muscles (pulley stations)</td>
<td></td>
<td>10–15 RM</td>
<td>† Strength knee extension, † Sitting to standing test, † Static Balance</td>
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<td>Large under extremity muscles (leg press and pulley stations)</td>
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<td>10–15 RM</td>
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<td>Step machine</td>
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<td></td>
<td>Aerobic + Balance</td>
<td></td>
<td>Static cycle</td>
<td>&gt; 15 min and &gt; 3 km</td>
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<tr>
<td>Exercise + Visual computer feedback</td>
<td>15 (80%)</td>
<td>81.5 (7.7) (69–95)</td>
<td>12</td>
<td>Strength +</td>
<td></td>
<td>Larger over extremity muscles (pulley stations)</td>
<td>10–15 RM</td>
<td>† Strength knee extension, † 6 minute walk test, † Training-specific performance</td>
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<td>Large under extremity muscles (leg press and pulley stations)</td>
<td>10–15 RM</td>
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<td>Aerobic + Balance</td>
<td></td>
<td>Static cycle</td>
<td>Standing, one-legged balance and walking on different surfaces (open and closed eyes)</td>
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<tr>
<td>363 Exercise Strength</td>
<td>31 (NA)</td>
<td>82.2 (4.1) (75–90)</td>
<td>12</td>
<td>Strength</td>
<td>3</td>
<td>Visual computer feedback</td>
<td>10x knee extensions</td>
<td>70–90% of maximal</td>
<td>† Leg extension strength, † Knee extension strength, † Knee flexion strength, † Ankle plantar flexion strength, † Handgrip strength, † Functional motor performance</td>
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<td>10x hip extension</td>
<td>70–90% of maximal</td>
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<td>10x left lifts</td>
<td>70–90% of maximal</td>
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<td>10x right lifts</td>
<td>70–90% of maximal</td>
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<td>15 lifts of bilateral plantar flexion (2–4 cm support)</td>
<td>45 min per training session</td>
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<td></td>
<td>Functional-Balance training + Physiotherapy</td>
<td>2</td>
<td>Multifactorial activities e.g., massaging or stretching</td>
<td>25 min</td>
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<tr>
<td>Control Placebo activities + Physiotherapy</td>
<td>26 (NA)</td>
<td>82.1 (4.8) (75–90)</td>
<td>12</td>
<td></td>
<td></td>
<td>Motor activities (e.g., flexibility, calisthenics, ball games and memory tasks)</td>
<td></td>
<td>1 hr</td>
<td>No effect during intervention and follow-up</td>
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<td>364 Exercise</td>
<td>62 (74%)</td>
<td>82.3 (6.6)</td>
<td>12</td>
<td>Strength</td>
<td>3</td>
<td>Relevant muscle group</td>
<td>70–80% 1RM</td>
<td>† Knee extension strength, † Knee flexion strength, † Ankle flexion strength, † Handgrip strength, † Functional performance</td>
<td>(continued)</td>
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Table 1. (CONTINUED)

<table>
<thead>
<tr>
<th>Reference</th>
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<th>n (% women)</th>
<th>Mean age (SD or range in years)</th>
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<th>Frequency (sessions/week)</th>
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<th>Exercises/session (repetitions per exercise)</th>
<th>Intensity/duration</th>
<th>Effects</th>
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<tr>
<td>Control</td>
<td></td>
<td>60 (73%)</td>
<td>82.9 (7.0)</td>
<td>12</td>
<td>Placebo activities</td>
<td>2</td>
<td>Flexibility exercise, calisthenics, low-intensity training with hand-held weights and ball games</td>
<td>5–10 min</td>
<td>No effect or ↓</td>
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<tr>
<td>365</td>
<td>Exercise</td>
<td>15 (80%)</td>
<td>88.5 (1.0) (85–98)</td>
<td>12</td>
<td>Strength</td>
<td>3</td>
<td>8x knee flexion + 8x knee extension</td>
<td>50% 1RM (0–2 weeks) 80% 1RM (2–12 weeks)</td>
<td>† 1RM</td>
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<td></td>
<td>↑ Isokinetic knee extension</td>
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<td>↑ Isometric knee extension</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>15 (73%)</td>
<td>90.9 (1.1) (85–98)</td>
<td>12</td>
<td>No PA</td>
<td></td>
<td></td>
<td></td>
<td>= 1RM</td>
<td></td>
</tr>
<tr>
<td>366</td>
<td>Exercise in long-term care-high mobility</td>
<td>22 (NA)</td>
<td>81.3 (5.3)* (85–98)</td>
<td>4</td>
<td>Warm-up/stretching + Aerobic + Strength Balance Cool-down/stretching</td>
<td>1–2</td>
<td>2–10 × lower body 2–10 × upper body</td>
<td>10 min</td>
<td>↑ Mobility</td>
<td></td>
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<td>↑ Balance</td>
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<td>↑ Flexibility</td>
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<td>↑ Knee strength</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Hip strength</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>14 (NA)</td>
<td>81.3 (5.3)* (85–98)</td>
<td>4</td>
<td>Warm-up/stretching + Aerobic + Strength Balance Cool-down/stretching</td>
<td>1–2</td>
<td>2–10 × lower body 2–10 × upper body</td>
<td>10 min</td>
<td>↑ Mobility</td>
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<td>↑ Balance</td>
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<td>↑ Flexibility</td>
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<td>↑ Knee strength</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Hip strength</td>
<td></td>
</tr>
<tr>
<td>Range of motion</td>
<td>32 (94%)</td>
<td>81.3 (5.3)* (85–98)</td>
<td>4</td>
<td>Introductions Vocal exercises Memory games Range of motions Relaxation exercises</td>
<td>5</td>
<td>Walking</td>
<td>10–15 min</td>
<td>↑ 10% weekly (maxi- mum 30 min) (Baseline intensity defined by each participant)</td>
<td>↑ Maximal walk endurance</td>
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<td>↑ Maximal walk distance (significant)</td>
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<td></td>
<td>= Hand-grip strength</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>= BMI</td>
<td></td>
</tr>
<tr>
<td>367</td>
<td>Exercise</td>
<td>19 (95%)</td>
<td>91.7 (6.3)</td>
<td>12</td>
<td>Aerobic</td>
<td>5</td>
<td>Walking</td>
<td>10 min</td>
<td>↑ Maximal walk endurance</td>
<td></td>
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<td></td>
<td>= Hand-grip strength</td>
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<td></td>
<td></td>
<td>= BMI</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>12 (100%)</td>
<td>89.3 (4.4)</td>
<td>12</td>
<td>Social control</td>
<td>1</td>
<td></td>
<td></td>
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(continued)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th>n (% women)</th>
<th>Mean age (SD or range in years)</th>
<th>Length (weeks)</th>
<th>Type</th>
<th>Frequency (sessions/week)</th>
<th>Sets</th>
<th>Exercises/session (repetitions per exercise)</th>
<th>Intensity/duration</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>368</td>
<td>Exercise</td>
<td>36 (81%)</td>
<td>83.7 (8) (67–98)*</td>
<td>24</td>
<td>Warm-up + Strength + Cool-down</td>
<td>2</td>
<td>Isometric exercises major muscle groups</td>
<td>10 min</td>
<td>↑ Quadriceps strength</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>29 (90%)</td>
<td>82 (9.6) (67–98)*</td>
<td>24</td>
<td>Reminiscence</td>
<td>2</td>
<td>Reminiscence therapy</td>
<td>10 min</td>
<td>↓ Quadriceps strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>369</td>
<td>Exercise</td>
<td>21 (90%)</td>
<td>81.4 (3.4) (75–96)*</td>
<td>24</td>
<td>Stretching + Range of movements exercises</td>
<td>1</td>
<td>5–10× each exercise</td>
<td>Support of a chair or work surface</td>
<td>45 min</td>
<td>No significant differences between the groups with regard to changes in any of the outcome variables (grip strength, ‘up &amp; go’ test, ‘sit to stand’ test, functional reach, spinal mobility, Barthel index, Philadelphia Geriatric Center Morale Scale)</td>
</tr>
<tr>
<td>Exercise</td>
<td>20 (85%)</td>
<td>82.9 (4.4) (75–96)*</td>
<td>24</td>
<td>Mobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trend towards improvement in comparison with control group (‘sit to stand’ and ‘up &amp; go’ tests)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>28 (89%)</td>
<td>81.9 (4.7) (75–96)*</td>
<td>24</td>
<td>Health education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant differences between the groups with regard to changes in any of the outcome variables (grip strength, ‘up &amp; go’ test, ‘sit to stand’ test, functional reach, spinal mobility, Barthel index, Philadelphia Geriatric Center Morale Scale)</td>
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<tr>
<th>Reference</th>
<th>Group</th>
<th>n (% women)</th>
<th>Mean age (SD or range in years)</th>
<th>Length (weeks)</th>
<th>Type</th>
<th>Frequency (sessions/week)</th>
<th>Sets</th>
<th>Exercises/session (repetitions per × exercise)</th>
<th>Intensity/duration</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>370</td>
<td>Exercise</td>
<td>39 (67%)</td>
<td>82.2 (1.3)</td>
<td>8</td>
<td>Strength + Balance + Functional mobility</td>
<td>3</td>
<td>5</td>
<td>Combined progressive exercises</td>
<td>1 hour</td>
<td>† 6-min walk test</td>
</tr>
<tr>
<td></td>
<td>WBV</td>
<td>38 (68%)</td>
<td>80 (1.4)</td>
<td>8</td>
<td>Vibration + Strength + Balance + Functional mobility</td>
<td>3</td>
<td>5</td>
<td>Whole body vibration</td>
<td>1 min 15–30 Hz 2–8 mm peak-to-peak</td>
<td>† 6-min walk test (greater improvements than exercise group)</td>
</tr>
<tr>
<td>371</td>
<td>Exercise</td>
<td>94 (81%)</td>
<td>87 (8)</td>
<td>32</td>
<td>Strength</td>
<td>5</td>
<td></td>
<td>Upper body resistance training (arm curls or arm raises)</td>
<td>Implement every 2 hr for a possible total of 4 care episodes per day</td>
<td>† Arm raise, † Arm curl, † Stands 30 sec</td>
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<td></td>
<td>75–90% of the maximal distance</td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>Control</td>
<td>96 (86%)</td>
<td>88 (7)</td>
<td>32</td>
<td>Mobility exercise + Stretching + Aerobic + Strength</td>
<td>2</td>
<td>1</td>
<td>Major muscle groups</td>
<td>40.45 min</td>
<td>† Meter walked or wheeled</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>20 (80%)</td>
<td>92 (2) (90–96)</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>† 1RM leg press (in participants with FAC &gt; 3)</td>
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<td></td>
<td></td>
<td>Rest periods</td>
<td>3</td>
<td>1</td>
<td>Cycling (cycle ergometer)</td>
<td>10–15 min</td>
<td>† Falls (1.2 fewer per participant than in the control group)</td>
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<td></td>
<td>Leg press exercise</td>
<td>2</td>
<td>3</td>
<td>10× biceps curls, arm extension, arm side lifts, shoulder elevations, seated bench presses and calf raises</td>
<td>30–70% 1RM († 5% weekly)</td>
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<td></td>
<td></td>
<td>3</td>
<td>1</td>
<td>1–3 kg or low-medium resistance bands</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>20 (80%)</td>
<td>92 (2) (90–97)</td>
<td>8</td>
<td>Mobility exercises in major muscle groups</td>
<td>5</td>
<td>1</td>
<td>Major exercise in major muscle groups</td>
<td>40–45 min</td>
<td>14 of 18 participants showed † RM leg press = Abilities to carry out instrumental activities of daily living</td>
</tr>
<tr>
<td>372</td>
<td>Exercise</td>
<td>34 (100%)</td>
<td>83.5 (4.1)</td>
<td>10</td>
<td>Warm-up + Strength +</td>
<td>2</td>
<td>2</td>
<td>8–30× knee extension 8–30× hip abduction</td>
<td>15 min</td>
<td>= Abilities to carry out instrumental activities of daily living</td>
</tr>
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<td></td>
<td>Functional exercises +</td>
<td></td>
<td></td>
<td>8–30× hip adduction</td>
<td>Gradually increased</td>
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<td>8–30× knee flexion</td>
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<td>15× exercise (e.g., rising from a chair or elbow flexion using light loads (1–2 kg))</td>
<td>30 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>34 (100%)</td>
<td>82.6 (3.7)</td>
<td>10</td>
<td>Relaxation Home exercise program</td>
<td>2</td>
<td>2</td>
<td>15× functional exercises</td>
<td>15 min</td>
<td>= Abilities to carry out instrumental activities of daily living</td>
</tr>
</tbody>
</table>

Of note, the mean age of the subjects in all the studies was ≥ 80 years.
*Data provided by the total number of participants.
BMI, Body mass index; CHO, carbohydrate; CSA, cross-sectional area; FAC, functional ambulation classification; NA, not available; PA, physical activity; RPE, rating of perceived exertion (Borg’s conventional scale, 6–20 points); 1RM, one repetition maximum; SD, standard deviation; SO, social activities; TG, training group; UCG, usual care group; WBV, whole-body vibration.
and leg lean mass (and thus likely to reduce risk fall) in postmenopausal women aged 50–75 years.88 Preliminary findings also support the potential effectiveness of including a weighted stair climbing exercise in the training programs of old people.89 Others, however, found no significant benefits of a home-based intervention using a weighted vest.90

Benefits of exercise in the frail elderly

Although numerous studies have shown the benefits of resistance training in old people in general, less research has focused specifically on the frail elderly. This is an important issue because frailty status might influence the potential applicability and effectiveness of the different training programs. For instance, Faber et al. found that fall-preventive, moderate-intensity, group exercise programs (mostly based on walking and balance exercises) had positive effects on fall risk and physical performance in pre-frail but not in frail elderly (mean age 85 years).91

Fiatarone et al. reported that physically frail, oldest old men and women improved their leg muscle strength outcomes by 220% after a 10-week strength training program (three sets of eight repetitions at 80% of 1RM, three times a week).80 Serra-Serra-Rexach et al. found an increment of 17% in the leg press strength of nonagenarians after 8 weeks of progressive strength training with lower loads (two to three sets of eight to 10 repetitions at 30% of 1RM in the initial phase progressing to 70% of 1RM at the end of the intervention).92 Lustosa et al. found significant improvements in the knee extensor muscle power of pre-frail elderly women after 12 weeks of strength exercises of the lower extremities at 70% of 1RM, three times a week.93 Although more research is needed, higher-intensity exercises seem to elicit higher gains. Thus, Sullivan et al.94 found greater increases in the muscle strength of frail elderly after a 12-week resistance training program of progressive intensity (starting at 20% and ending at 80% of 1RM) compared with a continuous, lower intensity protocol (20% of 1RM during the entire 12-week period).

The American College of Sports Medicine recommends a multi-component (strength, endurance, flexibility, and balance) exercise program to maintain physical fitness in old adults.95 Villareal et al. studied the effect of such a multi-component exercise program on physical fitness in frail, obese older adults during 3 months, finding beneficial effects on muscle mass and physical function.96 Lord et al. found significant improvements in choice stepping reaction time test, 6-min walking distance, and simple reaction time requiring a hand press, after training (aerobic exercises, specific strengthening exercises, and activities for balance, hand-eye and foot-eye coordination, and flexibility) during 12 months in frail older people living in retirement villages.97 Eshani et al.98 assessed the effect of a 6-month aerobic training program on frail elderly (consisting of walking at 70%–75% of maximal heart rate during 20 min at the initial phase and progressing to 60 min at the end of the program) and found a 14% of increase in VO2max.

Evidence on the benefits of exercise interventions in elderly with frailty, co-morbidities, and subsequent physical disability comes from a recent meta-analysis by deVries et al.99 This study included data on 18 randomized controlled trials (2,580 participants in total) of physical training interventions in community-dwelling adults aged 60–85 years who were physically frail and/or had physical disability and/or multi-morbidity. Half of the included studies used multi-component training programs, and intervention duration ranged from 5 weeks to 18 months. There were statistically significant benefits with physical exercise therapy compared to no exercise in mobility and physical functioning. There were no differences in effectiveness with regard to the duration of the program (short vs. longer interventions), whereas high-intensity programs elicited greater gains compared to low-intensity ones. The interventions that showed the largest effect sizes were those using resistance training components.

Benefits of exercise (particularly, resistance exercise) in the aging muscle tissue—main signaling pathways involved in exercise adaptations

The molecular mechanisms involved in the activation of signal transduction cascades regulating the adaptations to exercise are dependent on specific signaling pathways activated or repressed by numerous stimuli such as alterations in metabolites concentrations, adenosine triphosphate (ATP)-to-adenosine diphosphate (ADP) ratio, calcium flux, intracellular pH, redox balance, ROS production, and intracellular oxygen pressure.100–103 Post-exercise changes in gene transcription involve immediate early genes, myogenic regulators, genes that regulate carbohydrate metabolism and lipid mobilization, transport and oxidation, mitochondrial metabolism, and oxidative phosphorylation, as well as transcriptional regulators of gene expression and mitochondrial biogenesis,104–107 or alterations in the DNA-binding activity of a variety of transcription factors, such as myocyte enhancer factor 2 (MEF2), histone deacetylases (HDACs), and nuclear respiratory factors (NRFs).108 The most relevant signaling pathways modulated by exercise include calcium/calmodulin-dependent protein kinase (CaMKs) signaling, mitogen-activated protein kinases (MAPKs) signaling, ATP turnover and adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling, oxidized nicotinamide adenine dinucleotide (NAD+)/reduced nicotinamide adenine dinucleotide (NADH) ratio and sirtuins (SIRTs), activation of mammalian target of rapamycin (mTOR), oxygen sensing and the hypoxia-inducible factor 1 (HIF-1), mitochondrial biogenesis pathway, and the PPARγ co-activator-1α (PGC-1α) and $-1/β$(PGC-1/β).111 Accordingly, several important adaptations in skeletal muscle, such as mitochondrial biogenesis, anti-oxidant defense, hypertrophy, cytoprotection, and fiber transformation, are regulated primarily by these pathways. Below we summarize the main biological mechanisms and pathways through which exercise may attenuate sarcopenia (see also Fig. 2).

Calcium is implicated in the regulation of numerous intracellular proteins, such as protein kinase C, calcineurin, and CaMKs that mediate cellular signal transduction.112 Exercise increases CaMKII phosphorylation in an intensity-dependent manner, CaMKs and calcium signaling affect glucose transport,113 lipid uptake and oxidation,114 and skeletal muscle plasticity.115 In addition, the transcription factors cyclic AMP response element-binding protein (CREB), MEF2, and HDACs are CaMK targets involved in the regulation of skeletal muscle gene expression. Exercise
also stimulates MAPK-related pathways, including extracellular signal-regulated kinase 1 and 2 (ERK1/2),\textsuperscript{116} p38,\textsuperscript{117} and c-Jun NH\textsubscript{2}-terminal kinase (JNK).\textsuperscript{116} For instance, p38 MAPK can stimulate upstream transcription factors of the PGC-1\textalpha gene through skeletal muscle contraction.\textsuperscript{118} Moreover, MAPKs regulate a wide range of physiological processes, such as differentiation, hypertrophy, inflammation, and gene expression.\textsuperscript{119}

The role of ROS in the exercise-induced adaptations of skeletal muscles has been studied extensively, particularly with regard to aerobic exercise.\textsuperscript{120,121} Contracting skeletal muscles produce ROS, activating MAPK signaling and transcription factor nuclear factor-kappa B (NF-κB), thereby linking signal transduction to transcriptional processes.\textsuperscript{122} Acute exercise activates JNK signaling in a ROS-dependent manner, as evidenced by attenuated JNK signaling during exercise with infusion of the anti-oxidant N-acetylcysteine.\textsuperscript{123} Contraction-induced increases in interleukin-6 (IL-6) secretion, an exercise-associated cytokine with potent multi-organ metabolic effects\textsuperscript{124} (see further below), is JNK dependent,\textsuperscript{125} which attests to the likely importance of JNK signaling in mediating metabolic adaptations to exercise. AMPK is a serine/threonine kinase that modulates cellular metabolism acutely through phosphorylation of metabolic enzymes\textsuperscript{126} and, over time, via transcriptional regulation.\textsuperscript{127,128} Given the rate of ATP turnover during muscle contraction, AMPK acts as a signal transducer for metabolic adaptations by responding to an altered cellular energy status. Overall, AMPK activation preserves ATP by inhibiting both biosynthetic and anabolic pathways, while simultaneously stimulating catabolic pathways to re-establish cellular energy stores.\textsuperscript{129} Chronic AMPK activation modifies metabolic gene expression and stimulates mitochondrial biogenesis,\textsuperscript{127} partly via AMPK-induced modulation of the DNA-binding activity of transcription factors, including NRF-1, MEF2, and HDACs.\textsuperscript{127,130}
Sestrins are a recently discovered hallmark of aging sarcopenia. Mammalian cells express sestrins in response to stress including DNA damage, oxidative stress, and hypoxia. Sestrins can inhibit the activity of the mTOR complex 1 (mTORC1) through activation of AMPK.131 Sestrins prevent sarcopenia, insulin resistance, diabetes, and obesity. They also extend life span and health span through activation of AMPK, suppression of mTORC1, and stimulation of autphagic signaling.131 Recently, we proposed a possible role of the AMPK-modulating functions of sestrins in the benefits produced by exercise in older subjects.132

The regulation of the SIRT family of protein deacetylases is NAD$^+$ dependent.133 Both deacetylases SIRT1 and SIRT3 respond to elevations in [NAD$^+$] and the NAD$^+$/NADH ratio. Increased SIRT activity is associated with positive adaptations in skeletal muscle metabolism, including improved mitochondrial function and exercise performance.134,135 Likewise, the adaptive muscle growth consequent to mechanical loads induced by resistance exercise is largely determined by the enhanced skeletal muscle protein synthesis due to the activation of mTOR, ribosomal protein S6K (p70S6K), and downstream targets.136 p70S6K is a major regulator of muscle protein synthesis through pathways of protein translation and ribosome biogenesis involving eukaryotic translation initiation factor 4E (eIF4E), 4E binding protein 1 (4E-BP1), and elongation factor 2 (eEF2). Phosphorylation of 4E-BP1 by mTOR suppresses binding and inhibition of eIF4E by 4E-BP1. Phosphorylation of S6K leads to the phosphorylation of the 40S ribosomal protein S6 (rpS6) and eukaryotic translation initiation factor 4B (eIF4B). Collectively these events lead to the formation of the translation initiation complex and activate protein synthesis inducing cellular hypertrophy.137 Mechanosensory regulation of muscle protein synthesis also involves other signaling proteins, such as focal adhesion kinases (FAK), a class of transmembrane receptors that act as protein tyrosine kinases. FAK proteins are pivotal points for the transmission of contractile force throughout the skeletal muscle structure and a central component of integrin signaling. The grade of expression and activity of FAK in skeletal muscle is loading dependent,138,139 and contraction results in conformational modifications and activation of FAK phosphotransferase,138,140 which can trigger muscle protein synthesis through mTOR-dependent or -independent mechanisms.141

Oxygen sensing is also involved in the adaptations of skeletal muscle fibers to exercise, particularly aerobic exercise. Hypoxia-inducible factor (HIF), a heterodimeric transcription factor composed of two subunits (HIF-1α and HIF-1β), regulates the major signal transduction pathway sensitive to the intracellular partial pressure of oxygen. Activation of HIF-1 by many stimuli, including aerobic exercise, induces transcription of target genes involved in erythropoiesis, angiogenesis, glycolysis, and energy metabolism.105,142,143

Exercise benefits in neurodegeneration—main signaling pathways involved

Physical exercise produces important benefits in several neurodegenerative diseases.144,145 Here we focus on the effects of exercise in Alzheimer’s disease, which comprises per se 50%–56% of all causes of aging dementia (an additional 13%–17% is caused by Alzheimer’s disease combined with vascular diseases).146 Exercise, especially aerobic exercise, is beneficial for patients with Alzheimer’s disease,147 not only because it attenuates patients’ physical and psychosocial dependence but also because it improves several features of the pathophysiology of this disorder, including oxidative stress regulation, autophagy systems, neurotrophic signaling, mitochondrial biogenesis, angiogenesis, neurogenesis, and the modulation of specific amyloid-β (Aβ)-degrading enzymes (see Table 2 for a summary of intervention studies in humans and Fig. 3 for a summary of the putative molecular pathways involved).148,150

Oxidative stress plays an important role in the etiology of Alzheimer’s disease.151–154 The brain is especially sensitive to oxidative stress compared to other organs owing to its high metabolic rate (i.e., high O$_2$ consumption) together with its relatively low anti-oxidant defense capacity and its high levels of polyunsaturated fatty acids and metals.151,155 Elevated levels of brain oxidative stress are found with normal aging,156,157 and this phenomenon is exacerbated in Alzheimer’s disease due to additional sources of ROS such as Aβ accumulation and mitochondrial dysfunction.151,153,154,158 Although there is some controversy, aerobic exercise enhances anti-oxidant defense and mitigates oxidative damage in the brain of rodent models.159 Thus, exercise increases glutathione peroxidase (GPx) activity in whole brain,159 as well as superoxide dismutase (SOD) and GPx activity in the brainstem and corpus striatum.160 Using a triple transgenic mouse model of Alzheimer’s disease, we recently showed that aerobic exercise training can increase hippocampal catalse mRNA levels.161

Exercise attenuates aging neurodegeneration partly by up-regulating neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF).162,163 Circulating BDNF levels increase with aerobic exercise, especially when intensity is high.164–166 Exercise-produced BDNF can help maintain brain function and promote neuroplasticity,167,168 as well as repairing motor neurons.169 Increased BDNF transcripts in exercised rodents’ brains are well documented, which provides a biological explanation for the beneficial effect that exercise has in cognitive function, with tropomyosin receptor kinase (trkB), CREB, or synapsin I signaling being involved.170 These pathways are involved in synaptogenesis171 and long-term memory formation.172 Furthermore, the activation of the transcription factor CREB leads to induction of several genes that regulate neurotrophic effects, including those encoding PGC-1α,173 dynorphin, and BDNF.174 In addition, when the exercise induction of the BDNF pathway is blocked, aerobic exercise is unable to activate CREB and stimulate cognition.170,175 The hippocampal regulation of BDNF induced by exercise is mediated by neurotransmitters,167,176 neuroendocrine mechanisms,167 and insulin-like growth factor 1 (IGF-1) modulation.177,178 Thus, hippocampal IGF-1 levels increase with exercise training177 and have neurotrophic effects because IGF-1 activates BDNF signaling177 and increases trkB levels.179 Aerobic exercise induces other neurotrophic factors, such as vascular endothelial growth factor (VEGF),180 nerve growth factor (NGF),181 glial-derived neurotrophic factor (GDNF),182 neurotrophin (NT)-3,183 and NT-4/5,184 all of which act synergistically to induce neurogenesis and neuroplasticity.167,180
## Table 2. Summary of Controlled Exercise Interventions in Biomarkers of Neurodegeneration

<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th>Health status</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>373</td>
<td>High-intensity ET</td>
<td>Amnestic mild cognitive impairment</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Control (stretching)</td>
<td>Both</td>
<td>BDNF increased in men but decreased in women. ET group improved cognitive function compared to controls.</td>
</tr>
<tr>
<td>374</td>
<td>High-intensity ET</td>
<td>Glucose tolerance criteria for pre-diabetes or newly diagnosed</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Control (stretching)</td>
<td>Both</td>
<td>Although BDNF did not change, ET group improved cognitive functions compared to controls.</td>
</tr>
<tr>
<td>375</td>
<td>ET</td>
<td>Coronary artery disease</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td>No changes were observed in VEGF concentrations for both groups.</td>
</tr>
<tr>
<td>376</td>
<td>High-intensity ST</td>
<td>Healthy</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Moderate-intensity ST</td>
<td></td>
<td>IGF-1 increased in both ST groups.</td>
</tr>
<tr>
<td></td>
<td>Control (stretching)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>377</td>
<td>ST (non-frail)</td>
<td>Pre-frail and non-frail</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>ST (pre-frail)</td>
<td></td>
<td>BDNF increased in both groups. No changes in GDNF or NGF.</td>
</tr>
<tr>
<td>378</td>
<td>ET</td>
<td>Healthy</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Control (stretching)</td>
<td></td>
<td>ET increased the size of the hippocampus and BDNF.</td>
</tr>
<tr>
<td>379</td>
<td>ST</td>
<td>Healthy</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td>No changes on VEGF after ST</td>
</tr>
<tr>
<td>380</td>
<td>Combined</td>
<td>Obese</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td>VEGF increased after 12 weeks of combined training.</td>
</tr>
<tr>
<td>381</td>
<td>ET</td>
<td>Healthy</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>ST</td>
<td></td>
<td>Only ST increased BDNF</td>
</tr>
<tr>
<td>382</td>
<td>Combined (aerobic and resistance)</td>
<td>Healthy</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td>No changes in BDNF, ACE, APP, EGF, and TNF-α</td>
</tr>
<tr>
<td>383</td>
<td>Exercise + medical treatment</td>
<td>Peripheral artery disease</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Medical treatment</td>
<td></td>
<td>Exercise increased circulating EPC counts and decreased ADMA levels. No changes in VEGF and SDF-1.</td>
</tr>
<tr>
<td>384</td>
<td>Multi-modal (aerobic, strength and motor fitness)</td>
<td>Healthy</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td>Exercise increased BDNF and cognitive performance.</td>
</tr>
<tr>
<td>385</td>
<td>ET</td>
<td>Healthy</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Control (flexibility, toning and balance)</td>
<td></td>
<td>No changes in BDNF, IGF-1, VEGF</td>
</tr>
<tr>
<td>386</td>
<td>Acute exercise</td>
<td>intermittent claudication</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>ET</td>
<td>No change was observed in VEGF concentrations in response to acute exercise and to the training</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; APP, amyloid precursor protein; DMA, asymmetric dimethylarginine; BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor; EPC, endothelial progenitor cells; ET, endurance training; GDNF, glial-derived neurotrophic factor; IGF-1, insulin like growth factor 1; NGF, nerve growth factor; SDF-1, stromal cell-derived factor-1; ST, strength training; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.
Although neurons are post-mitotic cells, neurogenesis can still occur in specific areas of the adult hippocampus with some stimuli such as ischemia/reperfusion, aging, metabolic pathology, or physical exercise being able to change the rate of neurogenesis. Van Praag and collaborators have extensively studied the effects of exercise, particularly of the aerobic type, on adult neurogenesis and have demonstrated that the newly formed neurons are associated with the cognitive and synaptic effects induced by exercise. This phenomenon is especially important in age-related neurodegeneration because attenuation of accelerated neuronal loss can prevent several age-related disorders, including Alzheimer's disease. Several signaling pathways induced by aerobic exercise have been suggested to mediate this process such as BDNF, VEGF, and IGF-1.

FIG. 3. Main signaling pathways involved in the exercise effects in neurodegeneration, especially with regard to Alzheimer’s disease. 4-HNE, 4-hydroxynonenal; 8-OHdG, 8-hydroxy-2’-deoxyguanosine; Aβ, amyloid-β; BACE, β-secretase; BDNF, brain-derived-neurotrophic factor; IGF-1, insulin-like growth factor 1; LTP, long-term potentiation; MDA, malondialdehyde; RCD, reactive carbonyl derivative; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor. Color images available online at www.liebertpub.com/rej

Exercise and the Cellular Hallmarks of Aging

In a recent state-of-the-art review, López-Otín et al. nicely postulated nine hallmarks of aging that might be targeted in future pharmacological interventions—genomic instability, telomere attrition, epigenetic alterations, loss of protein homeostasis (proteostasis), deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.
Although more research is needed, exercise, which is available at low cost and largely free of adverse effects, can influence, at least partly, most of these hallmarks (see Fig. 1, right column, for a summary).

**Genomic instability**

A 5-month aerobic exercise program prevented mitochondrial DNA (mtDNA) instability in multiple tissues of mtDNA mutator (progeroid) mice, thereby reducing multistep pathology and preventing premature mortality. Oxidative damage to DNA occurs during the aging process. Resistance exercise decreases such damage in old people, as indicated by 8-hydroxy-2'-deoxyguanosine (8-OhdG) determination, through stimulation of endogenous anti-oxidant defense, whereas in rodent models aerobic exercise improves DNA repair mechanisms (e.g., proteasome complex), as well as NF-κB and PGC-1α signaling.

**Telomere attrition and telomerase activity**

Accelerated telomere shortening is linked with numerous age-related chronic diseases and risk factors. On the other hand, there is increasing evidence supporting an association between habitual physical exercise, particularly aerobic exercise, and longer leukocyte telomere length. Leukocyte telomere length is also positively associated with cardiorespiratory fitness (expressed as VO2max), which, in turn, is associated with lower CVD and all-cause mortality. Long-term aerobic exercise can modulate leukocyte telomere length as well as the network of proteins that interact with telomeres, through activation and induction of telomerase enzyme activity (mediated by human telomerase reverse transcriptase [TERT]) and the shelterin complex (or telosome). In effect, TERT mRNA expression is up-regulated in leukocytes after exercise. Exercise also regulates the microRNAs (miRNAs) that control the downstream expression of genes involved in telomere homeostasis. The association between physical exercise and telomere length could also be due to lower oxidative stress and inflammation, exercise-induced regulation of telomeric genes, or a complex interplay between these processes. The effects of exercise on skeletal muscle tissue telomeres have been less studied compared with leukocytes, and the results are less conclusive.

**Epigenetic adaptations**

The relationship between epigenetics regulation (e.g., DNA methylation) and aging is complex and controversial, i.e., hypomethylation or hypermethylation might be either beneficial or detrimental depending on the different cell types; and, whether manipulations of histone-modifying enzymes can influence aging through purely epigenetic mechanisms remains to be clarified. While keeping in mind the above-mentioned controversy, exercise seems to induce epigenetic modifications that can help attenuate age-deregulations, and several mechanisms, such as metabolic adaptations and transient hypoxia conditions, have been proposed recently. Regular aerobic exercise can modify genome-wide DNA methylation in humans. Animal and human research suggests that aerobic exercise induces, through epigenetic mechanisms, telomer-
epigenetic deregulation of growth factors in neurodegenerative diseases, not only by up-regulating BDNF induction as mentioned above, but also by promoting remodeling of the chromatin containing the BDNF gene.243

Overall, the study of exercise-induced epigenetic modifications is just in its infancy. Yet the studies available have already provided new insights into the potential tissue-specific alterations in DNA methylation induced by exercise and into some of the mechanisms explaining the beneficial effects of regular exercise.

Loss of proteostasis

Proteostasis is defined as the protein homeostasis that is responsible for refolding or degrading altered proteins by several mechanisms, such as autophagy, proteasomal degradation, or chaperone-mediated folding. A loss of function in these processes leads to an aggregation of damaged proteins and thereby proteotoxic effects that have been associated with aging76,246 and age-related conditions such as Alzheimer’s or Parkinson’s disease.247

The autophagy–lysosomal and the ubiquitin–proteasome systems, two important proteostatic mechanisms, are impaired by aging.248,249 Exercise has a beneficial effect in autophagy.250 In aging mouse models, aerobic exercise induces autophagy in: (1) The brain, supporting its potential to promote elimination of damaging proteins causing neurodegeneration251; (2) heart252; or (3) muscle (besides preventing apoptosis), by modulating IGF-1, Akt/mTOR, and Akt/Forkhead box O3A (FoxO3a) signaling, thereby preventing loss of muscle mass/strength.253,254 Although data are still scarce in aging humans, autophagy muscle markers are up-regulated after combined exercise training (walking and moderate-intensity leg resistance exercises) in old women.255

Aerobic exercise induces autophagy in mice through activation of the BCL-2–beclin-1 complex,256 whereas beclin-1 disruption in transgenic mice reduces autophagy leading to neurodegeneration.257 Moreover, the aging human brain shows a down-regulation of beclin-1,258 whereas healthy centenarians have higher serum levels of beclin-1 compared with young controls, suggesting that elevated basal levels of autophagy may be related to healthy human exceptional longevity.259 MacKenzie et al. showed that acute high-resistance exercise evoked increased muscle protein synthesis and decreased protein degradation in rats, through activation of the class 3 phosphatidylinositol 3OH-kinase (PI3K) Vps34 mVps34,260 which is known to regulate autophagy in these processes.260 Using an atrogin-1 (also known as MAPbx) knockout mouse model, Zaglia et al. demonstrated that autophagy dysfunction promotes cardiomyopathy and premature death.262 Atrogin-1 is a muscle-specific ubiquitin ligase involved in muscle atrophy through FoxO signaling.263

Similar to skeletal muscle, atrogin-1 up-regulation in the heart leads to atrophy.264 Interestingly, aged atrogin-1 knockout mice have reduced tolerance to treadmill exercise and shortened life span compared with age-matched controls.262 In this animal model, muscle age-related increases in oxidative damage and apoptosis are attenuated by regular aerobic exercise, whereas both mechanisms are negatively correlated with autophagy.261

Deregulated nutrient sensing

Exercise exerts protective effects against age declines in the glucose-sensing somatotrophic axis,265 and also activates at the muscle level the three main interconnected nutrient-sensing systems, i.e., the amino acid–sensing mTOR pathway266,267 and the low energy–sensing AMPK and SIRT pathways,132,268 thereby promoting a beneficial muscle anabolic state. On the other hand, exercise improves insulin sensitivity through increased production of the glucose transporter type 4 (Glut 4).269

In addition, resistance exercise acutely increases the circulating levels of testosterone, growth hormone (GH), and IGF-1, with the magnitude of the effect usually increasing with higher exercise intensity,270 or duration,271 shorter rest intervals,272 and higher exercising muscle mass.273,274 Thus, resistance exercise is a useful approach to prevent sarcopenia by virtue of its ability to increase protein synthesis275–277 and skeletal muscle mass.278,279 However, the rate of muscle protein synthesis in response to exercise training is lower in the elderly than in younger people,280,281 leading to a lower capacity to improve skeletal muscle strength and fiber size.282 On the other hand, supplementation with essential amino acids together with resistance training increases muscle protein synthesis both in young and old individuals, although such an effect is also attenuated in the latter, owing, at least partly, to lower ERK1/2 and mTOR signaling.280 (For a more extensive description about nutrient-sensing modulation by exercise, see above.)

Mitochondrial dysfunction

mtDNA mutations (typically deletions) accumulate with age in different tissues,283,284 including mainly the nervous and skeletal muscle tissue.37,285 Mutations in muscle mtDNA play a causal role in the physiological mechanisms implicated in sarcopenia,37–40 particularly in abnormalities of the electron transport system, muscle fiber atrophy, and breakage.37,39,40 Despite classic studies demonstrating exercise-induced mitochondrial biogenesis in young but not in aged mice,286 recent findings have shown that aerobic exercise training attenuates mitochondrial dysfunction and loss of mitochondrial content in the aging human skeletal muscle while increasing oxidative capacity and the activity of different electron transport chain protein complexes.287

The accumulated damage to the mitochondria due to the ROS generated from the electron transport chain is the base of the mitochondrial theory of aging first proposed by Harman.288 Oxidative damage to mtDNA increases with aging, affecting mtDNA replication and transcription, which, in turn, alters the functionality of mitochondrial proteins.289,290 Lanza et al. demonstrated that age-related decline in mitochondrial oxidative capacity was absent in endurance-trained humans, who showed elevated expression of mitochondrial proteins, mtDNA, and mitochondrial transcription factors.291 In mtDNA mutator mice, aerobic exercise promoted systemic mitochondrial biogenesis, prevented mtDNA depletion and mutations, increased mitochondrial oxidative capacity and respiratory chain assembly, restored mitochondrial morphology, and blunted pathological levels of apoptosis in multiple tissues. Thus, the authors concluded that a systemic “mitochondrial rejuvenation” occurred as a result of the training program.197
The lower mitochondrial enzyme activity commonly shown in older compared with younger adults\textsuperscript{17,292} is associated with a down-regulation of the mRNAs encoding mitochondrial proteins in skeletal muscle.\textsuperscript{293–295} Aged subjects have cytochrome c oxidase (COX)-deficient muscle fibers,\textsuperscript{296} especially in sarcopenic muscles or in those focal regions with higher content of mtDNA mutations.\textsuperscript{39,296–299} Yet resistance exercise training can reverse the muscle transcriptional signature of aging back to that of younger levels for most genes involved in mitochondrial function.\textsuperscript{209} Gomes et al.\textsuperscript{300} recently provided novel insights into the mechanisms responsible for the age decline of mitochondrial homeostasis by elegantly showing a regulatory pathway that is SIRT1-mediated and independent of PGC-1\textalpha{} and -\beta{}, with aging declining NAD\textsuperscript+ levels and thereby reducing SIRT1 activity and leading to impaired oxidative phosphorylation (OXPHOS). Short treatment (1 week, or \textsim{}8 months, when translated to the human life span) of 22-month-old mice with nicotinamide mononucleotide (NMN) (a precursor to NAD\textsuperscript+ increasing NAD\textsuperscript+ levels in vivo) reversed several biochemical indicators of muscle mitochondrial senescence, with increased OXPHOS transcripts in the gastrocnemius muscle. It was proposed that NMN or other compounds able to increase NAD\textsuperscript+ are candidates to be included in the human anti-aging armamentarium. And yet NMN, as opposed to exercise, was unable to reverse other age-dependent whole-organism effects, such as loss of muscle strength.

Besides the above-mentioned benefits of resistance exercise on muscle strength until end of life (which were summarized in Table 1), regular exercise has a profound beneficial effect on human mitochondrial function/biogenesis,\textsuperscript{301} with this effect being both PGC-1 and SIRT mediated.\textsuperscript{111} An active lifestyle attenuates aging mitochondrial dysfunction, promoting longevity through pathways common to the effects of caloric restriction.\textsuperscript{291} In addition, some “myokines” (see further below for the definition of myokine) have a mitochondrial rejuvenating effect, e.g., visfatin, a NAD\textsuperscript+ biosynthetic enzyme that stimulates the SIRT-1 pathway.\textsuperscript{252}

### Cellular senescence

Cellular senescence is defined as a stable arrest of the cell cycle coupled with stereotyped phenotypic changes, and its regulation during aging is a complex process. Indeed, the same phenomenon, i.e., elimination of senescent cells, that is beneficial to delay age-related pathologies and thus to promote longevity, could also stimulate cancer development.\textsuperscript{196} Besides inducing secretion of anti-tumorigenic myokines such as secreted protein acidic and rich in cysteine (SPARC, also known as basement membrane protein [BM]-40), calprotectin, or leukemia inhibitory factor,\textsuperscript{202} exercise, mainly aerobic exercise, may decrease cancer incidence and help improve cancer prognosis through several mechanisms, including greater natural killer (NK) cell activity, enhanced antigen presentation, reduced inflammation, and prevention of functional senescent cells’ accumulation.\textsuperscript{303} Telomere-associated proteins regulate cellular senescence and, as described above, are up-regulated by exercise. Moreover, aerobic exercise increases the aortic expression of telomere repeat-binding factor 2 and Ku70 and reduces the expression of apoptosis regulators, such as cell-cycle-checkpoint kinase 2, p16\textsuperscript{INK4a}, and p53 or survival regulators.\textsuperscript{216}

Telomere-associated proteins, as well as p16\textsuperscript{INK4a/Rb} and p19\textsuperscript{ARF}/p53 signaling, are considered main pathways in the control of human aging and age-associated pathologies.\textsuperscript{196} p16\textsuperscript{INK4a} and p21 are cell cycle inhibitors that are up-regulated in senescent cells.\textsuperscript{304,305} p21 is a downstream target of p53 and telomere dysfunction, whereas p16\textsuperscript{INK4a} appears to be up-regulated in a p53- and telomere-independent manner.\textsuperscript{306} Sousa-Victor et al. recently highlighted the importance of p16\textsuperscript{INK4a} in the modulation of cellular senescence. In a geriatric mouse model, muscle satellite cells lose their quiescent state owing to deregulation of p16\textsuperscript{INK4a}, whereas repressing p16\textsuperscript{INK4a} restores muscle regenerative capacity.\textsuperscript{307} Thus, we suggested the importance of p16\textsuperscript{INK4a} modulation as a new target for combating aging-related chronic diseases.\textsuperscript{308} Lifestyle factors, including smoking and physical aerobic exercise practice, have been associated with p16\textsuperscript{INK4a} mRNA levels in peripheral blood T lymphocytes,\textsuperscript{309} a biomarker of human aging.\textsuperscript{310} Thus, physical exercise is inversely correlated with p16\textsuperscript{INK4a} mRNA levels, i.e., higher amounts of physical exercise leads to down-regulation of p16\textsuperscript{INK4a} in blood cells, which might promote protective effects against age-dependent alterations.\textsuperscript{309}

As exposed above, cellular senescence plays a key role not only in cancer development\textsuperscript{311,312} but also in aging.\textsuperscript{313} In fact, cell senescence is one of the major paradigms of aging research through the acquisition of the senescence-associated secretory phenotype (SASP) or senescent-messaging secrectome.\textsuperscript{314} SASP is a DNA damage response, which, through production of inflammatory, growth-promoting, and remodeling factors can potentially explain how senescent cells alter tissue microenvironments.\textsuperscript{315} Different animal model investigations have shown that exercise modulates senescence associated to aging. Thus, 12 weeks of aerobic (swimming) exercise training suppressed liver senescence markers and down-regulated inflammatory mediators by reducing gamma glutamyltranspeptidase activity and levels of p53, p21, and IL-6 in a N-galactose-induced senescence rat model.\textsuperscript{316} Werner et al.\textsuperscript{225} studied the effect of aerobic exercise on telomere-regulating and cellular senescence mechanisms at the cardiac level in wild-type, endothelial NO\textsuperscript+ synthase (eNOS)-deficient and TERT-deficient mice models. Their results showed that exercise up-regulated cardiac telomere-stabilizing proteins, promoted anti-senescent effects, and provided protection against doxorubicin-induced cardiomyopathy. Werner et al.\textsuperscript{216} also studied the effects of aerobic exercise on vascular telomere biology and endothelial apoptosis in mice and the effects of long-term aerobic training on telomere biology in circulating leukocytes in humans. Besides improving telomere biology in the thoracic aorta and in mononuclear cells, exercise reduced the vascular expression of apoptosis regulators. Moreover, endurance athletes had increased telomerase activity and down-regulated cell cycle inhibitors compared with sedentary subjects. These findings are supported by Song et al.,\textsuperscript{309} who found that in humans aerobic exercise reduced the expression of DNA damage biomarkers and correlated positively with p16\textsuperscript{INK4a} expression and negatively with telomere length in peripheral blood T lymphocytes.
Stem cell exhaustion

The decline in the regenerative potential of tissues is a main characteristic of aging, whereas exercise is one of the most potent stimuli for the proliferation/migration of the different adult stem cell subsets from their home tissue (e.g., bone marrow) to target damaged tissues for subsequent engraftment and regeneration. Thus, regular exercise attenuates age-associated reduction in the endothelium-reparative capacity of endothelial progenitor cells. Exercise activates mesenchymal stem cells, which are pluripotent progenitors with a wide variety of therapeutic potential (e.g., as vehicles of anti-cancer genes) and promotes proliferation of neural stem cells, thereby contributing to improve brain regenerative capacity and cognitive ability.

Arguably the most affected stem cell type during aging is the myogenic one, known as satellite cells. Although the human skeletal muscle tissue maintains myofiber replacement and repair potential throughout most of life, the efficiency of this process declines with aging, owing to satellite cell alterations. Age-reduced number or functionality of these myogenic cells prevents proper maintenance of muscle mass. Specifically, aging atrophy of type II muscle fibers is accompanied by a specific decline in the content of type II muscle fiber satellite cells. Thus, since sarcopenia is associated with atrophy of type II muscle fibers, its pathophysiological mechanisms are closely related with the decline in satellite cell content with aging. Both aging reductions in muscle mass and strength are positively correlated with muscle fiber type specific cross-sectional area, myonuclear content, and satellite cell content.

Animal studies have demonstrated that aerobic exercise increases myofibers that contain higher numbers of satellite cells in both young and old rats, and also promotes expansion of the satellite cell pool in young and old mice. The contribution of these stem cells to skeletal muscle regeneration has been well documented. As stated by Hawke and Garry, because adult myofibers are postmitotic cells, the regulation of skeletal muscle is dependent on a small population of resident cells that are the satellite cells. The regulation of satellite cells involves several mechanisms, including immune response, neurotransmitters, neurotrophic and vascular factors (among other growth factors such as IGF-1), cytokines such as IL-6, testosterone, or NO, most of which are modulated by exercise.

Not only in young adults but also during aging, resistance training is able to induce skeletal muscle satellite cell proliferation and differentiation, thereby resulting in hypertrophy of type II fibers. The latter phenomenon, in turn, attenuates the pro-sarcopenic physiological events related to type II fiber atrophy associated with aging. On the other hand, although resistance training in the elderly of both sexes can counteract the loss of muscle mass and strength, a recent study reported that satellite cell induction in response to a single bout of resistance exercise is delayed in old men. McKay et al. also showed that, compared to young adults, muscle levels of myostatin, a protein that inhibits muscle differentiation and growth in the myogenesis process, were two-fold higher in older individuals, who also had 35% fewer basal stem cells and a type II fiber-specific impairment in stem cell content. The authors concluded that the co-localization of myostatin with satellite cells explains the worsened myogenic capacity of the aged skeletal muscle. In fact, an aging-blunted activation of type II muscle fiber satellite cells in response to an acute bout of resistance exercise was recently shown by Snijders et al. In addition, the satellite cell response to resistance exercise is related to the extent of muscular hypertrophy induced by training.

Altered intercellular communication

Aging is associated with altered intercellular communication leading to inflammation or “inflammaging.” Several mechanisms are responsible for this process, including accumulation of pro-inflammatory tissue damage, immune dysfunction, release of pro-inflammatory cytokines by senescent cells, higher activation of NF-κB, or impaired autophagy regulation. These events activate the NOD-like receptor protein 3 (NLRP3) “inflammasome,” characterized by elevations in IL-1β, tumor necrosis factor-α (TNF-α), and interferons. Interestingly, calorie restriction and exercise-mediated weight loss in obese individuals with type 2 diabetes lead to a reduction in adipose tissue expression of the NLRP3 inflammasome and IL-1β, and thus to reduced inflammation.

The decay factor AUF1 (AU-binding factor 1, also known as heterogeneous nuclear ribonucleoprotein D or hnRNP D) is implicated in the cessation of the inflammatory response (by mediating cytokine mRNA degradation) and also in the maintenance of telomere length by modulating TERT. Down-regulation of AUF1 leads to accelerated cellular senescence and premature aging in mice, which is rescued by normalizing the expression of this factor. Lai et al. found that chronic muscle contractile activity increased different AUF1 isoforms (p37, p40, and p45) in the muscle of healthy rats, resulting in improved muscle plasticity in response to subsequent contractile activity. Senescent cells transmit their condition to other cells through multiple mechanisms, including ROS, growth factors, and interleukins. As mentioned above, chronic physical exercise (mostly of the aerobic type) decreases ROS damage, and it does so by decreasing ROS production at the mitochondrial level while up-regulating endogenous anti-oxidant defense.

Importantly, skeletal muscle fibers produce hundreds of secreted factors or “myokines” (including the above-mentioned neurotrophins) with a potential drug-like effect at the local and systemic levels, i.e., proteins, growth factors, cytokines, or metalloproteinases, and this secretory capacity increases during and after exercise training (see Fiuzaluces for an in-depth review and Table 3 for some illustrative examples). Systemic low-level inflammation and related conditions such as CVD or cancer can be attenuated by the cumulative effect of regular exercise bouts, during which the muscle can release IL-6, arguably the myokine prototype. This, in turn, creates a healthy milieu by inducing the production of the anti-inflammatory cytokines IL-1 receptor antagonist (IL-1Ra), IL-10, or TNF soluble receptors (sTNFR) while inhibiting the pro-inflammatory cytokine TNF-α. The release of IL-6 from working muscles increases with exercise intensity and duration, and endogenous NO and the interaction between Ca/Ca2+/ nucleic factor of activated T cell (NFAT) and glycogen/p38 MAPK are the proposed upstream signals leading to its
<table>
<thead>
<tr>
<th>Name of molecule</th>
<th>Main tissue(s) of origin</th>
<th>Main type of exercise inducing its release/secretion</th>
<th>Main target tissue(s)</th>
<th>Main biological effect(s) associated with exercise-induced release/secretion</th>
<th>Main aging hallmark targeted</th>
<th>Potential future anti-aging application</th>
<th>Illustrative references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain-derived neurotrophic factor (BDNF)</td>
<td>Central nervous system, vascular endothelial cells, platelets, lymphocytes, eosinophils, monocytes, pituitary gland, working skeletal muscle</td>
<td>Moderate-intense &quot;aerobic&quot; exercise (e.g., brisk walking)</td>
<td>Brain, Motor neurons</td>
<td>↑ Neuroplasticity&lt;br&gt;↑ Motor unit regeneration</td>
<td>Cellular senescence in the brain</td>
<td>Protection against neurodegeneration (including possibly dementia)</td>
<td>167–169</td>
</tr>
<tr>
<td>Interleukin-4 (IL-4) and IL-13</td>
<td>Lymphocytes, mast cells and neutrophils</td>
<td>Resistance exercise (e.g., weightlifting)</td>
<td>Skeletal muscle</td>
<td>↑ Muscle growth</td>
<td>Loss of muscle proteostasis</td>
<td>Aging muscle atrophy/sarcopenia</td>
<td>387–389</td>
</tr>
<tr>
<td>IL-6 (also termed interleukin, beta 2)</td>
<td>Working muscles, Immune cells, Adipocytes</td>
<td>Intense ‘aerobic’ exercise (e.g., brisk/very brisk walking)</td>
<td>Skeletal muscle, Adipose tissue</td>
<td>↑ Muscle lipolysis&lt;br&gt;↑ Muscle growth&lt;br&gt;↑ Adipocyte lipolysis&lt;br&gt;↑ Liver-glucose release to blood&lt;br&gt;↑ Inflammation&lt;br&gt;↑ Immunomodulation</td>
<td>Altered inter-cellular communication (‘inflammaging’)</td>
<td>Age-related cardiometabolic diseases</td>
<td>129, 390–393</td>
</tr>
<tr>
<td>IL-15</td>
<td>Working muscles, Various origins (lymphoid tissues, kidney, brain, cardiac muscle, lung, pancreas, tests, liver, placenta, epithelial cells, and activated macrophages, and maybe adipocytes)</td>
<td>Mainly resistance exercise</td>
<td>Skeletal muscle, Adipose tissue</td>
<td>Promotes muscle anabolism/inhibits catabolism Anti-obesogenic (↓ mainly visceral fat) effect Insulin-sensitizing effect</td>
<td>Loss of muscle proteostasis</td>
<td>Aging muscle wasting/sarcopenia</td>
<td>394–397</td>
</tr>
<tr>
<td>Leukemia inhibitory factor (LIF)</td>
<td>Working muscles, Central nervous system</td>
<td>Mainly resistance exercise</td>
<td>Skeletal muscle, Mainly local (autocrine/paracrine effect):&lt;br&gt;↑ Muscle growth (satellite cell proliferation)&lt;br&gt;↑ Muscle regeneration</td>
<td>Main effects associated to myostatin inhibition which can be partly achieved by exercise are:&lt;br&gt;↑ Muscle growth&lt;br&gt;↑ Adiposity&lt;br&gt;↑ Insulin sensitivity</td>
<td>Loss of muscle proteostasis</td>
<td>Aging muscle wasting/sarcopenia</td>
<td>398–401</td>
</tr>
<tr>
<td>Myostatin (also termed, growth differentiation factor 8 [GDF8])</td>
<td>Skeletal muscle, Both “aerobic” and resistance exercise</td>
<td>Skeletal muscle, Adipose tissue</td>
<td>AMPK activation → ↑ sirtuin1 (SIRT1) → peroxisome proliferator-activated receptor γ (PPAR-γ)&lt;br&gt;It provides NAD⁺</td>
<td>Attenuation of disease/age muscle wasting Obesity/diabetes prevention</td>
<td>Use of exercise as a coadjuvant of myostatin-inhibition therapies for muscle wasting</td>
<td>402–406</td>
<td></td>
</tr>
<tr>
<td>Visfatin (also known as (nicotinamid phosphoribosyltransferase [NAMPT] or pre-B cell enhancing factor [PBEF])</td>
<td>Ubiquitous expression in human tissues, including adipose and skeletal muscle tissue (i.e., it is both an adipokine and a myokine), liver, bone marrow, lymphocytes, Β-cells and human islets, heart</td>
<td>&quot;Aerobic&quot; exercise</td>
<td>Skeletal muscle and adipose tissue</td>
<td>Mitochondrial dysfunction</td>
<td>Exercise as a major component of anti-aging medicine</td>
<td>407–410</td>
<td></td>
</tr>
</tbody>
</table>

The information provided in the table is based (and adapted from) a previous review paper by the authors.\(^{111}\)

AMPK AMP-activated protein kinase; NAD⁺, oxidized nicotinamide adenine dinucleotide.
secretion. Other anti-inflammatory myokines include IL-4, IL-10, or IL-13. Thus, life-long aerobic exercise training is associated with lower inflammation levels. Higher levels of aerobic exercise have also been associated with lower levels of C-reactive protein (CRP), IL-6, and TNF-α in people aged 70–79 years. However, although exercise training is known to have beneficial anti-inflammatory effects across a broad spectrum of organs and systems, more research is needed in the elderly, particularly to determine if the molecular mechanisms and pathways involved are similar in old people compared with younger population segments.

### Perspective

The benefits of regular exercise are such that a dose–response is usually observed in humans. Higher levels of moderate-to-vigorous exercise (≥450 min/week, clearly above the minimum international recommendations of 150 min/week) are associated with longer life expectancy. Furthermore, elite athletes—those humans sustaining the highest possible exercise levels (e.g., former participants in the Tour de France cycling race or former Olympic marathoners)—usually live considerably longer than the general population.

Physical exercise has a profound effect on the expression of a substantial proportion of our genome, which has evolved to optimize aerobic metabolism in an environment of food scarcity. Thus, physical inactivity is becoming a major public health problem worldwide. Exercise certainly cannot reverse the aging process, but it does attenuate many of its deleterious systemic and cellular effects. Most common age-associated chronic conditions are diseases of physiology and thus physiological interventions, of which physical exercise is arguably the best example, are largely the answer.

We propose that more research efforts should be devoted to gain insights into the molecular mediators of the exercise benefits. Besides putting more anti-aging drugs on the market, it would be wise to determine which are the most effective combinations, types, and dosages (frequency, duration, intensity) of exercise for older people and to implement efficient exercise interventions for this and younger population segments. **Note:** For the purposes of simplicity in this review, we have mostly used the common term “exercise” instead of “physical activity.”

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Address correspondence to: Fabian Sanchis-Gomar
Mitochondrial and Neuromuscular Diseases Laboratory
Research Institute of Hospital 12 de Octubre
(“i+12”) Avda. de Córdoba s/n
Madrid, 28041 Spain

E-mail: fabian.sanchis@uv.es
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