Aging Clin Exp Res (2017) 29:35–42
DOI 10.1007/s40520-016-0705-4

REVIEW

Physical activity and exercise as countermeasures to physical frailty and sarcopenia

Emanuele Marzetti[1] · Riccardo Calvani[1] · Matteo Tosato[1] · Matteo Cesari[2,3] · Mauro Di Bari[4,5] · Antonio Cherubini[6] · Marianna Broccatelli[1] · Giulia Savera[1] · Mariaelena D'Elia[1] · Marco Pahor[7] · Roberto Bernabei[1] · Francesco Landi[1] · on behalf of the SPRINTT Consortium

Received: 12 July 2016 / Accepted: 22 August 2016 / Published online: 8 February 2017

Abstract The identification of cost-effective interventions that improve the health status and prevent disability in old age is one of the most important public health challenges. Regular physical activity is the only intervention that has consistently been shown to improve functional health and energy balance and to reduce the risk of cardiovascular disease, stroke, diabetes, several cancers, depression and falls. In advanced age, physical activity is also effective at mitigating sarcopenia, restoring robustness, and preventing/delaying the development of disability. On the other hand, physical inactivity is recognized as one of the leading causes of several chronic degenerative diseases and is also a major contributing factor to sarcopenia and functional disability. This compelling evidence has prompted the World Health Organization to recommend engaging in regular physical activity throughout one's life course. The present review summarizes the available evidence in support of physical activity as a remedy against physical frailty and sarcopenia. The relevant pathways through which the benefits of physical activity are conveyed are also discussed.

Keywords Skeletal muscle · Physical performance · Exercise · Resistance training · Endurance training

✉ Emanuele Marzetti
emarzetti@live.com

✉ Francesco Landi
francesco.landi@rm.unicatt.it

1 Department of Geriatrics, Neurosciences and Orthopedics, Catholic University of the Sacred Heart School of Medicine, Rome, Italy

2 Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France

3 Université de Toulouse III Paul Sabatier, Toulouse, France

4 Research Unit of Medicine of Aging, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

5 Division of Geriatric Cardiology and Medicine, Department of Geriatrics and Medicine, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

6 Geriatrics and Geriatric Emergency Care, IRCCS-INRCA, Ancona, Italy

7 Department of Aging and Geriatric Research, University of Florida, Gainesville, FL, USA

Introduction

A sedentary lifestyle is the primary factor responsible for muscle weakness which, in turn, results in further reduction of activity levels and loss of muscle mass and strength [1]. In contrast, physical exercise is highly efficacious at counteracting the decline in muscle mass and strength associated with aging. Indeed, physical activity represents the most effective strategy currently available in the management of sarcopenia [1]. Even though there is not conclusive evidence to prescribe a specific exercise program in terms of type, intensity, frequency and duration, findings from randomized controlled trials (RCTs) have recently become available [1].

Here, the evidence in support of physical activity as a remedy for physical frailty and sarcopenia is presented, together with a concise overview of relevant physiologic pathways through which the benefits of exercise are conveyed.

Mechanisms of action and biological plausibility of physical activity

The mechanisms mediating the beneficial effects of physical activity on muscle health are multifold. The recruitment of muscle satellite cells is one of the most evident adaptations promoted by physical exercise [2, 3]. In fact, endurance and strength training provokes ultra-structural muscle damage and the subsequent release of inflammatory cytokines and growth factors—such as insulin like growth factor-1 (IGF-1), fibroblast growth factor (FGF) and mechano growth factor (MGF)—which stimulate the differentiation and proliferation of satellite cells [2, 3]. The incorporation of new nuclei from satellite cells into existing muscle fibers increases the number of "myonuclear domains" (i.e., the anatomical and functional units made up by a myonucleus and the surrounding volume of sarcoplasm), and therefore, the fiber cross-sectional area [4].

Aerobic exercise, which involves many repetitions and use of large muscle groups, increases energy production by mitochondria and capillary density, resulting in greater oxygen extraction and muscular endurance [5]. Muscle capillarity is increased to match the enhanced requirements of oxygen flux by muscle mitochondria. The muscle mitochondrial compartment can rapidly be expanded with endurance exercises, especially when subjects were previously sedentary. On the other hand, the fiber cross-sectional area is marginally affected by this exercise modality. Endurance exercise also induces innervation and metabolic perturbations that activate intermediate signaling pathways, including calcium-mediated signaling and metabolic sensing pathways such as AMP-activated protein kinase (AMPK) and sirtuin (SIRT) [2, 6]. These signals ultimately promote mitochondrial biogenesis and fatty acid transport and metabolism [2].

Resistance training, which involves few repetitions against moderate or high resistance and implies contraction of various muscle groups [7, 8], impacts mainly on muscle mass and strength. These gains are predominantly due to an increase in the size and number of myofibrils, with the fast-twitching fiber types (type IIA and IIX) being responsible for the greatest increase in muscle size [9]. Amelioration of insulin sensitivity, improved glucose utilization and enhanced myofibrillar protein synthesis are proposed mechanisms behind this effect of resistance exercise. Exercise-induced improvements in protein synthesis may also be due to nutrient-stimulated vasodilation and nutrient delivery to muscle rather than to ameliorations in insulin signaling [3].

Skeletal muscle contraction is associated with the production of reactive oxygen species (ROS). Exercise-induced ROS may serve as signaling molecules to stimulate cellular adaptation through the activation of redox-sensitive pathways, including NF-kB, MAP kinases, and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α). These signaling pathways mediate some of the effects of physical exercise, including mitochondrial biogenesis, antioxidant defense, inflammation, protein turnover, apoptosis, and autophagy [5].

The down-regulation of age-related chronic inflammation is another mechanism whereby exercise acts against age-dependent muscle decline and physical function impairment [1]. Indeed, the engagement in regular physical activity programs has been shown to reduce chronically elevated circulating levels of C-reactive protein and interleukin 6 [10].

Other lines of evidence indicate that physical activity mitigates the severity of myonuclear apoptosis [11], one of the mechanisms believed to be primarily responsible for muscle loss in late life [12], and improves the efficiency of myocytes quality control processes (e.g., autophagy, mitophagy and mitochondriogenesis) [13]. Indeed, apoptosis of skeletal myocytes has been proposed as a relevant target for interventions against physical frailty and sarcopenia [14].

Physical exercise interventions against sarcopenia

Several studies have explored the impact of exercise on sarcopenia [9, 15–20]. These investigations took into consideration muscle mass, muscle strength and physical performance measures, such as chair rise [16], 12-min walk test [17], stair climbing [7], or the timed up and go test [19, 20].

After 3–18 months of practice, resistance training interventions alone improved muscle mass in two out of four studies [9, 15] and muscle strength in three out of four studies [9, 15, 17] compared with control interventions (low-intensity home exercise or standard rehabilitation). Physical performance (chair rise, stair climb or 12-min walk) improved with resistance training alone versus the control in three studies that assessed this parameter [9, 16, 17].

Three additional studies explored compound exercise interventions (with different blends of aerobic, resistance, flexibility and/or balance training), which were performed for 3–18 months [18–20]. A high-intensity multipurpose exercise program over 18 months improved muscle mass, muscle strength and physical performance versus the control (successful aging) in a study in 246 women [19]. In two mixed-gender studies, muscle mass did not increase [18, 20]. Muscle strength improved with physical activity versus the control at 3 months of follow-up in one of the two studies [20], whereas physical performance did not improve in the one study in which it was assessed.

Goodpaster et al. [18] compared the effects of a combination of exercise programs (aerobic, strength, flexibility, and balance training) with a successful aging health educational program in 42 sedentary, community-dwellers (11 men and 31 women, mean age 77.1 ± 1.0 years). After 12 months, participants in the educational program group showed a significant loss of muscle strength which was completely prevented by the exercise program. Furthermore, an increase in muscle fat infiltration was documented in the control group, but not in the active intervention arm [18].

Fielding et al. [7] evaluated two different exercise programs in frail, community-dwelling older women (30 participants with a mean age of 73.0 ± 1.0 years) with self-reported physical disability. Fifteen participants were randomized to a 16-week high-velocity resistance training program, while the remaining enrollees were assigned to 16 weeks of traditional low-velocity resistance training. Improvements in lower extremity muscle power were greater in the high-intensity arm, despite similar increases in muscle strength in the two groups [7].

Campbell et al. [21] examined 29 healthy, sedentary persons (12 men and 17 women; age range: 54–78 years) randomized to three different 14-week interventions: sedentary control, lower-body resistance training, and whole-body resistance training. The two resistance training programs increased muscle strength and the mid-thigh muscle area in older people who consumed the appropriate amount of protein (0.8 g/kg of body weight per day). The lack of difference in response between the active intervention groups (lower and whole-body) suggests that the number of muscle groups trained did not influence exercise-induced muscle hypertrophy.

Marques et al. [22] demonstrated that a training program with weight-bearing exercises for 8 months decreased fat mass and improved muscle strength, postural sway, and bone mineral density in a sample of 60 women aged 60–95 years. Hence, this intervention was effective at ameliorating potential risk factors for falls and related fractures.

Based on the available evidence, recommendations for frail older people should include a balanced program of both endurance and strength exercises performed on a regular schedule (at least 3 days a week) [1]. However, it is important to bear in mind that specific modifications to these recommendations may be necessary in persons with co-existing medical conditions or special needs.

Physical exercise intervention against physical frailty and disability

Physical inactivity is a major risk factor for physical frailty and disability in older adults [23]. Conversely, regular physical activity extends lifespan and reduces the risk of disability [24]. Physical activity started in late life continues to improve functional independence and reduces mortality, maintaining a strong effect even after controlling for potential confounders, such as smoking, hypertension, obesity, and family history of cardiovascular diseases, cancer or diabetes [25–27].

The largest and longest study in this field is the Lifestyle Interventions and Independence for Elders (LIFE) study, a multicenter RCT recently conducted in the United States [28]. In LIFE, the efficacy of a physical activity program in preventing disability was assessed in more than 1600 sedentary and functionally limited older persons, over a follow-up of approximately 3 years in comparison with a successful aging educational program. The full-scale trial was designed based on the promising results of the LIFE pilot (LIFE-P) [29], in which 424 sedentary older persons at risk for disability engaged in moderate-intensity physical activity or a successful aging intervention for an average of 1.2 years. The major eligibility criterion for both LIFE-P and the full-scale RCT was the presence of physical function impairment, defined as a Short Physical Performance Battery (SPPB) [30] summary score ≤9. In both trials, the primary outcome was the incidence of mobility disability, operationalized as incident inability to walk 400 meters within 15 min without sitting, help of another person or use of a walker [28, 29]. The physical activity program consisted of a combination of walking at moderate intensity, resistance exercises, balance, stretching and behavioral counseling. The successful aging educational program consisted of health education seminars and upper extremity stretching exercises. Results from the LIFE-P showed that, over 1 year of follow-up, the incidence of major mobility disability was lower and the SPPB score was increased in the exercise group [29]. The beneficial effects of the intervention on the SPPB score and the 400-m walk test were fairly uniform across subgroups defined by age, gender, ethnicity, baseline physical performance, and comorbidity.

Secondary analyses of the LIFE-P conducted on a subgroup of participants who underwent DXA for body composition at enrollment and at 12 months ($n = 177$) showed that the physical activity program conferred comparable benefits to older persons with and without sarcopenia [31]. Notably, the physical activity intervention reduced the prevalence and severity of physical frailty, with greater effects in participants who were frailer at baseline [32].

The LIFE full-scale RCT confirmed and extended the findings of LIFE-P by showing that the physical activity intervention reduced the risk of developing mobility disability by 18% relative to the control group [28]. The results did not significantly differ when participants were categorized by ethnicity/race, gender, history of cardiovascular disease, history of diabetes, or cognition. Remarkably, participants with lower physical function at baseline (i.e., SPPB < 8) were those who mostly benefited from the intervention.

Overall, these results support the proposition that a specific physical exercise program—namely, a combination of endurance and resistance exercises—is effective in preventing mobility disability and ameliorating the frailty status in older adults at risk of disability.

Exercise protocol in SPRINTT

The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) project is being conducted under the auspices of the Innovative Medicines Initiative (IMI) [33]. In SPRINTT, the efficacy of a multicomponent intervention (MCI), based on long-term structured physical activity, nutritional counseling/dietary intervention and an information and communication technology (ICT) intervention, for preventing mobility disability is tested in comparison with a healthy aging lifestyle education (HALE) program in community-dwelling older persons with physical frailty and sarcopenia [33].

The physical activity program, described in the following subsections, has been designed based upon the LIFE study exercise protocol [34], given its full safety profile and efficacy at preventing mobility disability in at-risk older persons.

Components of training

The physical activity program includes aerobic, strength, flexibility, and balance training. The program focuses on walking as the primary mode of physical activity for preventing/postponing major mobility disability (primary outcome), given its widespread popularity and ease of administration across a broad segment of the older population. Other forms of endurance activity (e.g., stationary cycling) are utilized when regular walking is contraindicated medically or behaviorally. Each session is preceded by a brief warm-up and followed by a short cool-down period. Following each bout of walking, participants perform flexibility exercises.

Three times per week, following a bout of walking, participants have been instructed during the initial phase of the program to complete a 10-min routine focused primarily on lower extremity muscle strengthening (Table 1). Supplementary instructional materials (e.g., videotapes, printed materials) have been supplied to participants to reinforce the strength training occurring during supervised training, so that it can be generalized to the home environment. In addition, the intervention involves encouraging participants to increase all forms of physical activity throughout the day. This includes activities such as leisure sports, gardening, the use of stairs as opposed to escalators/elevators, and walks with friends.

Intensity of training

Participants are introduced to the physical activity program in a structured way such that they begin with lighter intensity and gradually increase intensity over the first 2–3 weeks of the intervention. Walking for physical activity is promoted at a moderate intensity. The rating of perceived exertion (RPE) is used as a method to regulate physical activity intensity. Using the Borg's scale (range 6–20), participants are asked to walk at an intensity of 13 (activity perception of "somewhat hard"). They are instead discouraged from exercising at levels that approach or exceed 15 ("hard") or drop to a rating of 11 ("fairly light") or below. Lower extremity strengthening exercises are performed at an intensity of 15–16 ("hard").

Frequency and duration of training

The physical activity program consists of continuing twice-per-week center-based group exercise sessions and a progression of home-based physical activity to 3–4 times per week (Table 1). The intervention comprises a general weekly walking goal of 150 min. This is consistent with the public health message from the Physical Activity Guidelines for Americans report that states that moderate physical activity should be performed for 30 min on most if not all days of the week (150–210 total minutes) (http://health.gov/paguidelines/pdf/paguide.pdf). This goal is approached in a progressive manner during the first 3 months of the trial in an individualized manner, according to the physical abilities and limitations of each participant. Center-based sessions are supplemented, in a progressive fashion, with home-based exercises as a means of promoting physical

Table 1 Mode and frequency of physical activity in SPRINTT

Phase	Center-based physical activity	Home-based physical activity
Adoption (weeks 1–52)	Twice weekly	1 time/week (weeks 1–4) 2 times/week (weeks 4–8) Up to 3–4 times/week (weeks 8–52)
Maintenance (week 52—end of the trial)	Twice weekly	Up to 3–4 times/week

activity in multiple settings to aid behavioral generalization and long-term adherence.

Aerobic component of the physical activity intervention

As previously mentioned, walking is the primary mode of physical activity in SPRINTT. Participants have been taught to assess their RPE using the Borg's scale. Walking pace is promoted at a moderate intensity (RPE = 13). If the RPE drops below 11 or exceeds 15, the participant's walking pace is adjusted accordingly. A typical physical activity session is composed of a 5-min warm-up consisting of low intensity walking (RPE < 9) or, when walking cannot be performed at an RPE < 9, stationary cycling. Participants then complete walking and strength training at the target RPE for each activity for the amount of time prescribed. At the end of each physical activity session, there are 3 minutes of cool down in which the walking speed is gradually reduced.

Strength training component of the physical activity intervention

Strength training focuses primarily on five lower extremity exercises (Table 2). Adjustable ankle weights have been provided to all participants. The goal is to include three sessions of strength training (RPE = 15–16) throughout the intervention. Each strength exercise includes two sets of ten repetitions each, with 1-min rest in between. The target intensity is approached in a progressive manner over a 4-week period depending on the progress of each participant. At each exercise session, participants complete one strength training exercise from all of the five groups, for a total of five exercises (Table 2).

Balance training protocol

Participants perform balance training according to five different levels of difficulty. Progression to the next level

Table 2 Strength training exercises in SPRINTT

Exercise	Execution mode
Group 1	
Wide leg squat	Participant stands in front of a chair, aims their buttocks into the chair and slowly lowers themselves into a seated position; pause for a breath in the seated position; participant stands up slowly pushing up from their heels through their lower legs, thighs, hips, and buttocks
Group 2 (with ankle weights)	
Standing leg curl	Participant stands behind a chair. Keeping thighs side-by-side, participant lifts their foot up towards the buttocks until the upper and lower leg forms a 90° angle (2 sets of 10 repetitions for each leg)
Hip extension	Participant stands behind a chair with hands resting along the top of the chair back. Participant slowly lifts one leg straight back without bending their knee and holds the position for 1 s (2 sets of 10 repetitions for each leg)
Hip flexion	Participant stands in the same position as the hip extension exercise. Participant slowly bends the knee towards their chest, without bending at the waist or hips, and holds the position for 1 s (2 sets of 10 repetitions for each leg)
Group 3 (with ankle weights)	
Knee extension	Participant is to sit back in a chair. Keeping the foot flexed, the participant raises one leg until it is fully extended (2 sets of 10 repetitions for each leg)
Knee extension and ankle circles	Participant is in the same position and moves their leg as described before. With the knee as straight as possible, participants rotate their right ankle 5 times to the right, and then 5 times to the left (2 sets of 10 repetitions for each leg)
Group 4	
Side hip raise	Participant stands straight with feet together and hands resting on the back of a chair. Keeping their toes pointed straight ahead, participant lifts one leg out to the side until their foot is 15–20 cm off the ground (2 sets of 10 repetitions for each leg)
Leg circles	Participant stands up straight with feet together and their side towards the back of the chair. Keeping their foot flexed, the participant lifts one leg until their foot is 15–20 cm off the ground, then makes large clockwise circles, while keeping their foot lifted and leg extended (5–10 circles for each leg)
Group 5	
Toe stand	Participant stands straight with feet together and hands resting on the back of a chair. The participant slowly raises their body as high as possible on the balls of their feet (2 sets of 10 repetitions)
Toes out calf raise	Participant stands behind a chair with feet slightly apart and then points their toes out to the side, with hands resting on the back of the chair. Participant raises their body on the balls of their feet (2 sets of 10 repetitions)

occurs when all exercises of a certain level can be performed correctly. Balance exercises are performed once a day every day throughout the intervention.

Upper body exercises

Upper body exercises are incorporated at the end of the session (Table 3). Each month, one upper body exercise is chosen by the trainer and performed at the end of the group session.

Conclusion

Physical activity, in its various blends, increases aerobic capacity, muscle mass, strength and endurance by ameliorating aerobic conditioning and/or strength [35]. Indeed, the most recent recommendations advise people of all ages to include a minimum of 30 min of moderate intensity physical activity (such as brisk walking) on most, if not all, days of the week [35]. For most people, greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or longer duration. Notably, in older persons, physical activity confers at least the same beneficial as in younger individuals [36].

Accumulating evidence supports regular physical activity, in combination with appropriate nutritional support, as the most effective strategy for improving sarcopenia and physical function and preventing disability [37]. Nevertheless, whether the positive effects of exercise interventions can be sustained for an adequate duration of time and maintained at sufficient intensity to prevent incident disabilities is presently unclear [38, 39].

The SPRINTT trial will provide evidence of the efficacy of long-term moderate-intensity physical activity, as part of a MCI, in preventing mobility disability and several adverse health outcomes in older persons with physical frailty and sarcopenia, who are at risk of disability. SPRINTT will be the largest and longest trial of its kind performed in Europe and its findings are expected to promote significant advancements in the management of frail older persons with sarcopenia from both clinical and healthcare perspectives.

Acknowledgements The present work was funded by a grant from the Innovative Medicines Initiative—Joint Undertaking (IMI-JU 115621). The work was also partly supported by the "Centro Studi

Table 3 Upper-body exercises in SPRINTT

Exercise	Execution mode
Exercise 1: Wall push-up	Participant stands facing wall approximately 60 cm away and places their palms flat on the wall. Participant leans towards the wall, keeping their elbows tucked in until their nose is almost touching the wall. After holding this position for 1 s, the participant returns to the starting position until their arms are straight (10 repetitions)
Exercise 2: Bicep curl	Participant stands or sits in a chair while holding an ankle weight in one hand, with their palm facing forward. Keeping the wrist straight, the participant raises their forearm up towards their chest and holds this position for 1 s. The participant brings their arm back down slowly, keeping their hands facing their chest (10 repetitions)
Exercise 3: Arm raise	Participant stands with feet hip-width apart while holding an ankle weight in each hand. The participant raises both arms forward into a "Y" position with thumbs facing up. After holding this position for 1 s, the participant returns to the starting position (10 repetitions)
Exercise 4: Chair push (triceps extension)	Participant sits in a chair with armrests. Participant grabs the arms of the chair with each hand and pushes slowly off the chair. After holding this position for 1 s, the participant returns to the starting position (10 repetitions)
Exercise 5: Triceps kickback	Participant stands with feet hip-width apart while holding an ankle weight in each hand. Participant brings their arm back slowly past their hips or as far as comfortable, keeping their elbow straight. After holding this position for 1 s, the participant returns to the starting position (10 repetitions)
Exercise 6: Tennis ball squeeze	Participant sits holding a tennis ball in one hand. Participant gently squeezes the tennis ball and holds the position for 5 s (10 repetitions)
Exercise 7: Lawn mower pull	Participant sits with feet shoulder-width apart holding an ankle weight with the hand crossed over to the opposite hip with their palm facing inwards. Participant lifts their arm up and across their body ending with the palm facing outwards. After holding this position for 1 s, the participant returns to the starting position (10 repetitions)
Exercise 8: Seated neck turn	Participant sits up straight in a chair with their feet flat on the ground, head facing forward, and a towel or pillow supporting the lower back. Participant turns their head slowly to the right as far as is comfortable. After holding the position for 1 s, the participant brings their head slowly back to the starting position; then, the participant turns their head slowly to the left as far as is comfortable, holding the position for 1 s (5 repetitions)

Achille e Linda Lorenzon" (E.M., R.C.), Fondazione Roma (NCDs Call for Proposals 2013; E.M., R.C.), and intramural research grants from the Catholic University of the Sacred Heart (D3.2 2013 and D3.2 2015; E.M., F.L., M.T., R.C.).

Compliance with ethical standards

Conflict of interest All of the authors are partners of the SPRINTT consortium, which is partly funded by the European Federation of Pharmaceutical Industries and Associations (EFPIA). E.M. served as a consultant for Huron Consulting Group, Genactis, and Novartis. M.C. served as a consultant for and/or received honoraria for scientific presentations from Nestlé.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study informed consent is not required.

References

1. Landi F, Marzetti E, Martone AM, Bernabei R, Onder G (2014) Exercise as a remedy for sarcopenia. Curr Opin Clin Nutr Metab Care 17:25–31. doi:10.1097/MCO.0000000000000018
2. Thornell LE (2011) Sarcopenic obesity: satellite cells in the aging muscle. Curr Opin Clin Nutr Metab Care 14:22–27. doi:10.1097/MCO.0b013e3283412260
3. Kang JS, Krauss RS (2010) Muscle stem cells in developmental and regenerative myogenesis. Curr Opin Clin Nutr Metab Care 13:243–248. doi:10.1097/MCO.0b013e328336ea98
4. Calvani R, Joseph AM, Adhihetty PJ, Miccheli A, Bossola M, Leeuwenburgh C, Bernabei R, Marzetti E (2013) Mitochondrial pathways in sarcopenia of aging and disuse muscle atrophy. Biol Chem 394:393–414. doi:10.1515/hsz-2012-0247
5. Marzetti E, Lawler JM, Hiona A, Manini T, Seo AY, Leeuwenburgh C (2008) Modulation of age-induced apoptotic signaling and cellular remodeling by exercise and calorie restriction in skeletal muscle. Free Radic Biol Med 44:160–168. doi:10.1016/j.freeradbiomed.2007.05.028
6. Rowe GC, Safdar A, Arany Z (2014) Running forward: new frontiers in endurance exercise biology. Circulation 129:798–810. doi:10.1161/CIRCULATIONAHA.113.001590
7. Fielding RA, LeBrasseur NK, Cuoco A, Bean J, Mizer K, Fiatarone Singh MA (2002) High-velocity resistance training increases skeletal muscle peak power in older women. J Am Geriatr Soc 50:655–662. doi:10.1046/j.1532-5415.2002.50159.x
8. Paillard T, Lafont C, Soulat JM, Costes-Salon MC, Mario B, Montoya R, Dupui P (2004) Neuromuscular effects of three training methods in ageing women. J Sports Med Phys Fitness 44:87–91
9. Suetta C, Andersen JL, Dalgas U, Berget J, Koskinen S, Aagaard P, Magnusson SP, Kjaer M (2008) Resistance training induces qualitative changes in muscle morphology, muscle architecture, and muscle function in elderly postoperative patients. J Appl Physiol (1985) 105:180–186. doi:10.1152/japplphysiol.01354.2007
10. Beyer I, Mets T, Bautmans I (2012) Chronic low-grade inflammation and age-related sarcopenia. Curr Opin Clin Nutr Metab Care 15:12–22. doi:10.1097/MCO.0b013e32834dd297
11. Marzetti E, Groban L, Wohlgemuth SE, Lees HA, Lin M, Jobe H, Giovannini S, Leeuwenburgh C, Carter CS (2008) Effects of short-term GH supplementation and treadmill exercise training on physical performance and skeletal muscle apoptosis in old rats. Am J Physiol Regul Integr Comp Physiol 294:R558–R567. doi:10.1152/ajpregu.00620.2007
12. Marzetti E, Privitera G, Simili V, Wohlgemuth SE, Aulisa L, Pahor M, Leeuwenburgh C (2010) Multiple pathways to the same end: mechanisms of myonuclear apoptosis in sarcopenia of aging. Sci World J 10:340–349. doi:10.1100/tsw.2010.27
13. Wohlgemuth SE, Lees HA, Marzetti E, Manini TM, Aranda JM, Daniels MJ, Pahor M, Perri MG, Leeuwenburgh C, Anton SD (2011) An exploratory analysis of the effects of a weight loss plus exercise program on cellular quality control mechanisms in older overweight women. Rejuvenation Res 14:315–324. doi:10.1089/rej.2010.1132
14. Marzetti E, Calvani R, Bernabei R, Leeuwenburgh C (2012) Apoptosis in skeletal myocytes: a potential target for interventions against sarcopenia and physical frailty—a mini-review. Gerontology 58:99–106. doi:10.1159/000330064
15. Binder EF, Yarasheski KE, Steger-May K, Sinacore DR, Brown M, Schechtman KB, Holloszy JO (2005) Effects of progressive resistance training on body composition in frail older adults: results of a randomized, controlled trial. J Gerontol A Biol Sci Med Sci 60:1425–1431. doi:10.1093/gerona/60.11.1425
16. Bonnefoy M, Cornu C, Normand S, Boutitie F, Bugnard F, Rahmani A, Lacour JR, Laville M (2003) The effects of exercise and protein-energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study. Br J Nutr 89:731–739. doi:10.1079/BJN2003836
17. Bunout D, Barrera G, de la Maza P, Avendano M, Gattas V, Petermann M, Hirsch S (2001) The impact of nutritional supplementation and resistance training on the health functioning of free-living Chilean elders: results of 18 months of follow-up. J Nutr 131:2441 S–2446 S
18. Goodpaster BH, Chomentowski P, Ward BK, Rossi A, Glynn NW, Delmonico MJ, Kritchevsky SB, Pahor M, Newman AB (2008) Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. J Appl Physiol (1985) 105:1498–1503. doi:10.1152/japplphysiol.90425.2008
19. Kemmler W, von SS, Engelke K, Haberle L, Mayhew JL, Kalender WA (2010) Exercise, body composition, and functional ability: a randomized controlled trial. Am J Prev Med 38:279–287. doi:10.1016/j.amepre.2009.10.042
20. Rydwik E, Lammes E, Frandin K, Akner G (2008) Effects of a physical and nutritional intervention program for frail elderly people over age 75. A randomized controlled pilot treatment trial. Aging Clin Exp Res 20:159–170. doi:10.1007/BF03324763
21. Campbell WW, Trappe TA, Jozsi AC, Kruskall LJ, Wolfe RR, Evans WJ (2002) Dietary protein adequacy and lower body versus whole body resistive training in older humans. J Physiol 542:631–642. doi:10.1113/jphysiol.2002.020685
22. Marques EA, Mota J, Machado L, Sousa F, Coelho M, Moreira P, Carvalho J (2011) Multicomponent training program with weight-bearing exercises elicits favorable bone density, muscle strength, and balance adaptations in older women. Calcif Tissue Int 88:117–129. doi:10.1007/s00223-010-9437-1
23. Booth FW, Roberts CK, Laye MJ (2012) Lack of exercise is a major cause of chronic diseases. Compr Physiol 2:1143–1211. doi:10.1002/cphy.c110025
24. Landi F, Abbatecola AM, Provinciali M, Corsonello A, Bustacchini S, Manigrasso L, Cherubini A, Bernabei R, Lattanzio F (2010) Moving against frailty: does physical activity matter? Biogerontology 11:537–545. doi:10.1007/s10522-010-9296-1
25. Landi F, Russo A, Cesari M, Pahor M, Liperoti R, Danese P, Bernabei R, Onder G (2008) Walking one hour or more per

day prevented mortality among older persons: results from ilSIRENTE study. Prev Med 47:422–426. doi:10.1016/j.ypmed.2008.06.020
26. Grassi C, Landi F, Delogu G (2014) Lifestyles and ageing: targeting key mechanisms to shift the balance from unhealthy to healthy ageing. Stud Health Technol Inform 203:99–111. doi:10.3233/978-1-61499-425-1-99
27. Vetrano DL, Martone AM, Mastropaolo S, Tosato M, Colloca G, Marzetti E, Onder G, Bernabei R, Landi F (2013) Prevalence of the seven cardiovascular health metrics in a Mediterranean country: results from a cross-sectional study. Eur J Public Health 23:858–862. doi:10.1093/eurpub/ckt130
28. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, Espeland MA, Fielding RA, Gill TM, Groessl EJ, King AC, Kritchevsky SB, Manini TM, McDermott MM, Miller ME, Newman AB, Rejeski WJ, Sink KM, Williamson JD (2014) Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. JAMA 311:2387–2396. doi:10.1001/jama.2014.5616
29. Pahor M, Blair SN, Espeland M, Fielding R, Gill TM, Guralnik JM, Hadley EC, King AC, Kritchevsky SB, Maraldi C, Miller ME, Newman AB, Rejeski WJ, Romashkan S, Studenski S (2006) Effects of a physical activity intervention on measures of physical performance: results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. J Gerontol A Biol Sci Med Sci 61:1157–1165
30. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB (1994) A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 49:M85–M94. doi:10.1093/geronj/49.2.M85
31. Liu CK, Leng X, Hsu FC, Kritchevsky SB, Ding J, Earnest CP, Ferrucci L, Goodpaster BH, Guralnik JM, Lenchik L, Pahor M, Fielding RA (2014) The impact of sarcopenia on a physical activity intervention: the Lifestyle Interventions and Independence for Elders Pilot Study (LIFE-P). J Nutr Health Aging 18:59–64. doi:10.1007/s12603-013-0369-0
32. Cesari M, Vellas B, Hsu FC, Newman AB, Doss H, King AC, Manini TM, Church T, Gill TM, Miller ME, Pahor M (2015) A physical activity intervention to treat the frailty syndrome in older persons-results from the LIFE-P study. J Gerontol A Biol Sci Med Sci 70:216–222. doi:10.1093/gerona/glu099
33. Marzetti E, Calvani R, Landi F, Hoogendijk EO, Fougere B, Vellas B, Pahor M, Bernabei R, Cesari M (2015) Innovative Medicines Initiative: the SPRINTT Project. J Frailty Aging 4:207–208
34. Fielding RA, Rejeski WJ, Blair S, Church T, Espeland MA, Gill TM, Guralnik JM, Hsu FC, Katula J, King AC, Kritchevsky SB, McDermott MM, Miller ME, Nayfield S, Newman AB, Williamson JD, Bonds D, Romashkan S, Hadley E, Pahor M (2011) The lifestyle interventions and independence for elders study: design and methods. J Gerontol A Biol Sci Med Sci 66:1226–1237. doi:10.1093/gerona/glr123
35. Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T (2014) Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 43:748–759. doi:10.1093/ageing/afu115
36. Martone AM, Lattanzio F, Abbatecola AM, Carpia DL, Tosato M, Marzetti E, Calvani R, Onder G, Landi F (2015) Treating sarcopenia in older and oldest old. Curr Pharm Des 21:1715–1722. doi:10.2174/1381612821666150130122032#sthash.xBO96OL5.dpuf
37. Calvani R, Miccheli A, Landi F, Bossola M, Cesari M, Leeuwenburgh C, Sieber CC, Bernabei R, Marzetti E (2013) Current nutritional recommendations and novel dietary strategies to manage sarcopenia. J Frailty Aging 2:38–53
38. Landi F, Calvani R, Cesari M, Tosato M, Martone AM, Bernabei R, Onder G, Marzetti E (2015) Sarcopenia as the biological substrate of physical frailty. Clin Geriatr Med 31:367–374. doi:10.1016/j.cger.2015.04.005
39. Bernabei R, Martone AM, Vetrano DL, Calvani R, Landi F, Marzetti E (2014) Frailty, physical frailty, sarcopenia: a new conceptual model. Stud Health Technol Inform 203:78–84. doi:10.3233/978-1-61499-425-1-78