Calcif Tissue Int (2016) 98:531–545
DOI 10.1007/s00223-016-0107-9

REVIEW

# Rationale for Strengthening Muscle to Prevent Falls and Fractures: A Review of the Evidence

Olivier Benichou[1] · Stephen R. Lord[2]

Received: 30 September 2015 / Accepted: 4 January 2016 / Published online: 4 February 2016


**Abstract** Falls represent a major public health problem in older people, predominantly due to the resulting injuries which lead to progressive disability, immobilization and resulting comorbidities, dependency, institutionalization, and death. Reduced muscle strength and power have been consistently identified as risk factors for falls and related injuries, and it is likely these associations result from the central role played by reduced muscle strength and power in poor balance recovery. In addition, muscle strength and power are involved with protective responses that reduce the risk of an injury if a fall occurs. Progressive resistance training (PRT) is the standard way to increase muscle strength and power, and this training forms one of the main components of fall prevention exercise interventions. However, PRT has rarely been implemented in routine practice due to multiple challenges inherent to frail older people. The ongoing development of drugs expected to increase muscle power offers a new opportunity to reduce the risk of falls and fall-related injuries. The intent here is not to replace exercise training with drugs but rather to offer a pharmacologic alternative when exercise is not possible or contraindicated. The target population would be those most likely to benefit from this mechanism of action, i.e., weak older people without major causes for falls independent of muscle weakness. Provided such a tailored strategy was followed, a muscle anabolic may address this major unmet need.

✉ Olivier Benichou
benichouol@lilly.com

[1] Eli Lilly and Company, 24, Boulevard Vital-Bouhot, 92200 Neuilly, France

[2] NeuRA, UNSW, Sydney, NSW, Australia

**Keywords** Muscle · Strength · Power · Balance · Fall · Injury · Fracture

## Introduction

Muscle strengthening is among the main pillars of standard of care to prevent falls in older people but its efficacy is limited by multiple challenges inherent to the target population. The current development of drugs intended to increase muscle mass and power offers an unprecedented opportunity to overcome these limitations and further reduce the risk of falls and injuries. This paper first reviews the importance of the unmet need for fall prevention. It then summarizes the published evidence supporting the concept that increasing muscle power should result in a lower risk of falls and related injuries. Then, after describing the efficacy and limitations of the standard of care to prevent falls, the manuscript offers a brief overview of the drugs that are being developed to increase muscle mass and power and could therefore be candidates for development in the indication to prevent falls and related injuries. Finally, it concludes with considerations about the population tailoring strategy for clinical development in such an indication and about some of the risks associated with this development.

## Consequences of Falls in Older People

### The Burden of Falls in Older People

Falls represent a major public health problem in older people, predominantly due to the resulting injuries which lead to progressive disability, immobilization and associated comorbidities, dependency, institutionalization, and death [1–3].

Thirty percent of community-dwelling persons older than 65 years fall at least once per year, and 15 % fall at least twice per year [4]. This incidence doubles in people beyond 75 years of age, as well as in older people living in residential aged care [2].

In addition to falling frequently, older people also have a high susceptibility to injury due to slowed reflexes, impaired protective responses when falling and comorbidities such as osteoporosis [2]. It is estimated that 20 % of falls result in injuries requiring medical attention [3]. In 2013, in the US, 2.5 million non-fatal falls among older adults were treated in emergency departments and more than 734,000 of these patients were hospitalized [5]. In 2006, injurious falls accounted for 1 in 10 emergency department visits among patients aged 65 years and older in the US [6]. The most common injuries were fractures (41.0 %), superficial contusion/injuries (22.6 %), and open wounds (21.4 %) [6], while other significant consequences include joint dislocations and potentially lethal traumatic brain injuries [3, 7]. In 2013, the direct medical costs of falls, adjusted for inflation in the US were $34 billion [8].

Fear of falling also has a major impact on quality of life in older people [9–12]. Older persons often reduce their physical activity after falls, which leads to physical deconditioning, social isolation, and reduced quality of life [10, 13]. In fact, falls appear to be the largest single cause of restricted activity among older adults, accounting for 18 % of restricted activity days in this group (National Health Interview Survey [2].

Due to all these factors, falls and, to a greater extent, recurrent falls represent a strong predictor of long-term admission to residential aged care facility [14]. Ultimately, unintentional injuries are the 5$^{th}$ leading cause of death in older adults (after cardiovascular disease, cancer, stroke, and pulmonary disorders), and falls constitute two-thirds of these deaths, representing the 6$^{th}$ leading cause of death in the elderly [2]. The death rates from falls among older men and women have risen sharply over the past decade; in 2013, about 25,500 older adults died from unintentional fall injuries in the US [5].

## How Important are Falls to Fractures?

A fracture occurs when the energy conveyed to a bone (by a fall or another trauma or activity) exceeds bone strength (Fig. 1). This means that preventing a fracture could focus on increasing bone strength, reducing the risk of falls, or reducing the energy transmitted to bone by falls, or ideally all three of the above. Over the last decades, fracture prevention has focused primarily on increasing bone strength in people with osteoporosis rather than on preventing falls. As pointed out by Jarvinen et al., it is time to “shift the focus in fracture prevention from osteoporosis to falls” [15]. Here are the main reasons:

Osteoporosis drugs prevent only a minority of the non-vertebral fractures (NVFx), even in patients with osteoporosis. In pivotal trials, anti-osteoporosis drugs reduced the risk of NVFx by ~15–50 % (20–30 % for the most widely used bisphosphonates), and vertebral fractures (VFx) by ~35–70 % (~50 % for the most widely used bisphosphonates), although these numbers vary according to the drug considered [16]. This means that 50–85 % of NVFx still occur despite anti-osteoporosis treatment, even in a context of pivotal trials where treatment compliance is much higher than in routine practice [17, 18].

While it was previously considered that bone mineral density (BMD) accounts for the majority of the risk for NVFx [19], evidence collected from large cohorts suggests the opposite, at least above the age of 65 years [20]. In the Study of Osteoporotic Fractures, only 15 % of low trauma NVFx were attributable to osteoporosis as defined by a hip or spine BMD *T* score $\leq -2.5$, and only 25 % of NVFx were attributable to a T score below $-1.5$ [21]. A more recent study performed in 1126 women older than 70 years showed a population attributable risk of NVFx of ~30 % for a *T* score BMD below $-1$ [22].

The overwhelming majority of NVFx result from a fall: i.e. 96–100 % of wrist fractures, 95–97 % of humerus fractures, and 92–96 % of hip fractures [23–25]. This very strong link between NVFx and falls is especially important when considering that (1) the vast majority of fractures are peripheral in the elderly, and (2) NVFx have the greatest consequences on health and health care costs. Indeed, almost all NVFx are symptomatic as compared to only 22–33 % of VFx [26–29]. In addition to reducing quality of life for several months, NVFx lead, especially in older people, to immobilization-related comorbidities (thromboembolism, pneumonia, urinary sepsis, etc.) which account for the high rate of death after hip fracture especially [30–32]. Hip fractures alone were estimated to cost 20 billion USD in the US in 2003 [33], a figure excluding other costly NVFx such as fractures of the wrist, humerus, ribs, and pelvis [34, 35].

These dramatic figures underline the importance of addressing falls to reduce the risk of fracture and to extend fall and fracture prevention efforts beyond osteoporotic populations.

A fall from standing height should not be considered as a minor trauma since it delivers an amount of energy that substantially exceeds the force required to break a femur or distal radius [23, 36–39]. Despite this, only ~5 % of the falls in older people result in a fracture [4]. It has been postulated that the following four characteristics play a key

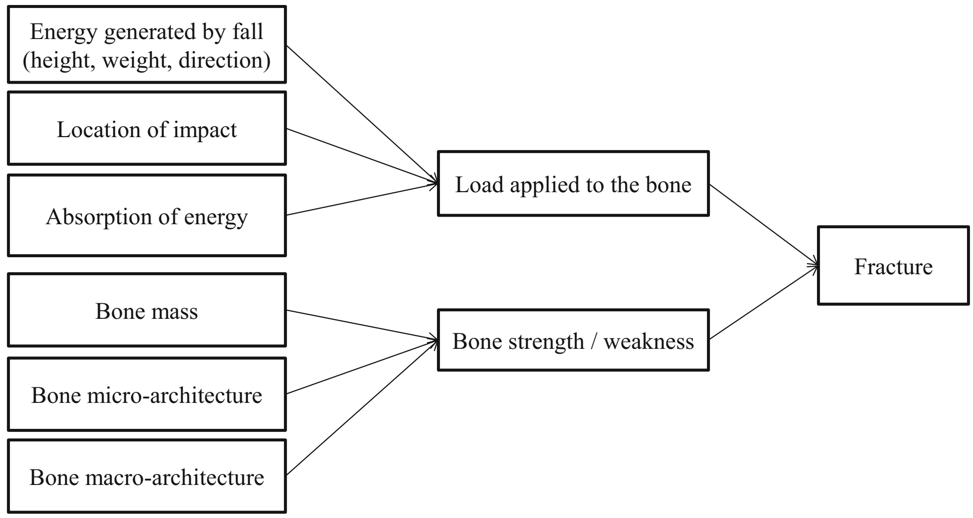


**Fig. 1** Respective roles of fall energy and bone weakness contributing to a fracture. A fracture occurs when the load generated by a fall (or another trauma or activity) exceeds bone resistance

role in whether a fall will or will not result in a fracture [23]:

- Location of impact (driven by direction of the fall and sometimes voluntary movements).
- Energy generated by the fall (combination of mass and velocity at impact).
- Absorption of energy (protective response, soft tissue over the bone, and ground hardness).
- Bone strength (geometry, quality, and density).

Because muscle strength is not only an important determinant in the occurrence of falls (hence to the resulting energy) but also of the direction of falls (hence to location of impact) and of the efficacy of protective responses (hence to absorption of energy), increasing muscle strength in older people at high risk may reduce not only the incidence of falls but also the incidence of related injuries including fractures.

## Observational Studies: Muscle Weakness is Consistently and Strongly Associated with the Risk of Falls and Related Injuries

A high number of causes and risk factors for falling have been identified. These include older age, history of falls, muscle weakness, dementia, neurologic disorders, visual impairment, medication use (especially sedative drugs and antidepressants), orthostatic hypotension, environmental hazards, fear of falling, gait characteristics (reduced stride length and velocity), and lower limb pain [2, 40–42].

Muscle weakness has been measured by various means. These include measurement of specific muscle groups (i.e., grip, knee extension, or hip abductor muscles) or multiple muscle groups (leg press). Muscle performance has also been assessed under isometric and dynamic (isokinetic) conditions and measured as strength (peak force) or power (rate of force development). Finally, strength and power have been inferred from functional assessments such as repeated chair rise and stair climbing speed.

Moreland et al. [43] conducted a systematic review and meta-analysis of studies evaluating muscle weakness as a potential risk factor for falls (studies published in up to 2002). For lower extremity weakness, the combined OR was 1.76 (95 % confidence interval 1.31–2.37) for any fall and 3.06 (95 % CI 1.86–5.04) for recurrent falls. For upper extremity weakness, the combined OR was 1.53 (95 % CI 1.01–2.32) for any fall and 1.41 (95 % CI 1.25–1.59) for recurrent falls [43]. Since then, other studies have confirmed the importance of muscle weakness as one of the main risk factors for falls [2, 44–53]. This consistent association between muscle weakness and the risk of falls is demonstrated not only for single and recurrent falls, but also for injurious falls and for fall-related fractures [23, 54–63]. Falls are also predicted by low muscle or lean mass [64, 65] but the relationship between fractures and muscle/lean mass is less firmly established [66–68].

## Muscle Strength and Power Play Central Roles in Balance Recovery

In order to maintain balance when it is threatened or simply during activities of daily living, we assess our position relative to the environment through the sensory (afferent) system (visual, vestibular, and proprioceptive functions) and adjust our body position and muscle tone accordingly with the efferent system (Fig. 2) [45, 69, 70]. The efferent system comprises the peripheral nerves that link with the

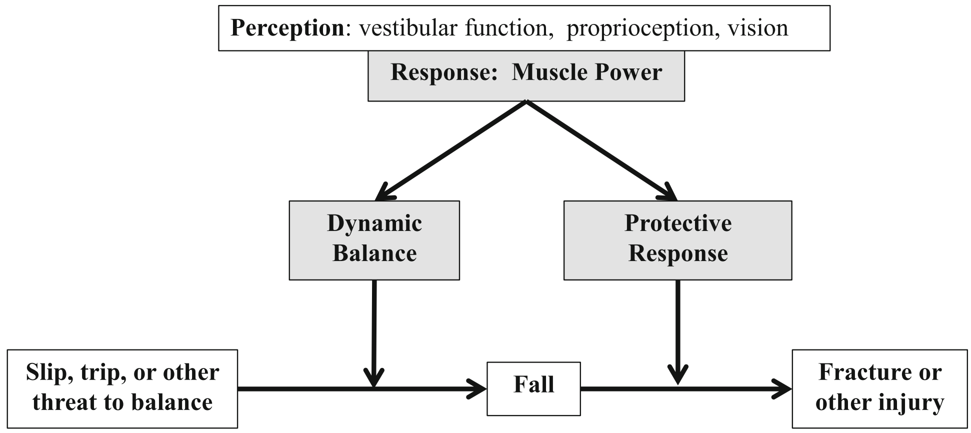


**Fig. 2** Central role of muscle power in the process of fractures or other injuries. Lack of muscle power increases the risk of injurious falls mainly by impairing: (1) dynamic balance (ability to recover and prevent a fall when balance is threatened), and (2) protective responses intended to minimize and/or avoid injury upon falling

muscular system to generate postural adjustments including corrections required after a perturbation to stance or gait [45]. Therefore, although muscle weakness is only one of numerous causes for falls, it plays a crucial role in determining whether or not a fall will occur following a balance perturbation [45, 69, 71]. For instance, muscle weakness can predispose to falls by preventing an effective correcting step when slipping or by impairing foot clearance when negotiating an obstacle [71, 72].

An illustration of the critical role of muscle strength and power in balance comes from the very high propensity to falls observed in disorders affecting mostly or exclusively the muscular system such as inclusion body myositis [73], muscular dystrophy [74, 75], and myotonic dystrophy [76, 77].

Various perturbations have been used in biomechanical studies to elucidate balance recovery mechanisms. These perturbations have included trips on obstacles [71], slips on slippery floor surfaces [69], floor translations [78, 79], level changes during walking [80], and tether release from a leaning angle [81–83]. Several of these studies confirmed the important role of lower limb muscle strength and power in the ability to recover successfully from a balance challenge [69, 71, 78, 81, 84, 85]. It has also been shown that trunk muscle strength [86] and arm strength [87–93] play complementary significant roles in balance recovery.

## Muscle Power is Particularly Critical to Balance Recovery and Decreases Rapidly with Age

Muscle power is the rate of force development, whereas as strength is the production of a maximal contraction independent of time. Muscle power has been shown to be more important than muscle strength not only for physical function [94, 95] but also for dynamic balance [96], which is not surprising since the time needed to take corrective actions when balance is threatened is critical to the ability to conduct an appropriate corrective strategy, such as a protective step [97].

Lower limb muscle strength and power decrease progressively from early adulthood to end of life [98–101]. There is no commonly accepted definition for "muscle weakness" based on leg strength, but the prevalence of muscle weakness based on hand grip strength (FNIH definition) increases ten-fold between the ages of 60–79 years (2 %) and 80 years and over (19 %) [102]. Causes for decreased muscle strength/power include any cause of muscle atrophy as well as disorders of the peripheral and central nervous systems. Age-associated muscle atrophy is considered as multifactorial, with neurologic (central nervous system atrophy, degeneration of neuromuscular junctions, and motor unit loss/reorganization) [103], endocrine (decreased production of growth hormone and insulin growth factor-1, hypogonadism, and insulin resistance), inflammatory (high level of inflammatory cytokines), nutritional (denutrition), hereditary, and behavioral origins (reduced physical activity) with some comorbidities playing a key role in this process as described later in this paper [104, 105].

Age-associated muscle wasting involves a decrease in the size and number of type I and II fibers, with a differentially higher loss of type II fibers. Type II muscle fibers are fast twitched, mostly anaerobic, and have a larger cross-sectional area than type I fibers which are mostly aerobic and contract more slowly [106]. Therefore, type II fibers are better suited for movements requiring explosive muscle power (such as regaining posture after a balance perturbation, rising from a chair, or climbing steps) while type I fibers are more prominent in muscles involved in endurance. As a result, the age-associated decrease in muscle power is even larger than the decrease in isometric strength, especially between the 7th and 9th decades of life [97, 99, 107–109].

Therefore, while age-associated muscle wasting impacts various aspects of muscle performance, it effects particularly (although not exclusively) muscle power which is key to avoiding fall-related injuries through dynamic balance and protective responses. As a result, when assessing the mechanism of action of potential candidate drugs to be tested for fall prevention, it will be important to determine their respective effects on muscle power versus strength.

## Safe Landings: Muscle Strength and Power are Key to the Ability to Develop Protective Responses When Falling

Muscle weakness (of both the lower and upper limbs) is predictive of whether the impact of a fall will result in an injury [110–112]. This association is likely due to weaker people having less efficacious protective responses during a fall. Thus, they are unable to use either their upper limbs or body movements for avoiding direct impact on critical or fragile parts of the body such as the greater trochanter or the head [113, 114]. Such protective responses explain why only 5 % of falls result in a fracture, despite the high amount of energy delivered by a fall from a standing height [2, 3, 23, 37].

Protective responses have been studied in multiple settings that are often specific to one fall direction (forward, sideways, or backward) since this direction determines not only the nature of the resulting injuries but also the strategy developed by older people to avoid them. Breaking falls with movements of the upper limbs is a common strategy irrespective of the fall direction and requires substantial muscle power to be effective in preventing fractures [37, 114–117]. In the Study of Osteoporotic Fractures, it was observed that fallers who broke a fall by hitting or grabbing an object were three times less likely to have a hip fracture compared to those who did not [112]. During sideways falls, a quick rotation of the trunk enables fallers to avoid a direct shock on the hip [37, 79] which is a critical determinant of whether or not a fall will result in a hip fracture [38, 112, 118]. During backward falls, it is suggested that pelvis velocity at impact is substantially reduced by an eccentric contraction of lower limb muscles which absorb the energy of the fall [37, 119] and that a decrease in lower limb muscle strength reduces the effectiveness of this protective response and increases impact severity [119].

## Role of Muscle Wasting in the Downward Spiral of Falls and Related Injuries

Older people suffer more serious injuries as a result of a fall [120], and they recover more slowly which results in longer periods of reduced activity compared to younger people [2]. Reduced activity, often aggravated by fear of falling, leads to deconditioning, muscle atrophy, and weakness, which in turn further increases the risk of subsequent falls and injuries [10, 121–123]. This step by step downward spiral (Fig. 3) is well recognized and explains partly why history of falls is a strong independent risk factor for future falls [2, 10, 122, 124]. Besides falls and related injuries, this downward spiral of deconditioning often involves other events such as a sepsis, a cardiac event, or a chronic obstructive pulmonary disease (COPD) exacerbation, which also result in bed rest, decreased physical activity, further disuse atrophy and muscle weakness. Therefore, even if falls constitute only one of these possible events on the path to motor impairment and frailty, they represent not only a cause but also a consequence of muscle atrophy and weakness.

In addition, inability to rise from the floor is common in older people [125], contributes to complications after a fall [126], and is a significant risk factor for fall-related injury [127–129]. The contribution of muscle weakness to this inability to get up from the floor [129–131] emphasizes another important objective of muscle strengthening in frail elderly.

## Effects of Progressive Resistance Training (PRT) on Balance, Falls, and Injuries

Resistance exercise training is the current standard way to increase muscle strength and power in older people with reduced muscle performance [132]. Its magnitude of efficacy varies from one study to another, with indications that high-velocity PRT is particularly efficacious in improving muscle power [133]. The overall findings, however, are consistently positive [134, 135].

### Effects of PRT on Measures of Balance

As of 2008, 29 clinical studies had evaluated the effects of PRT on various measures of balance and were the topic for a detailed Cochrane review [136]. The vast majority of these studies assessed balance as a secondary or exploratory endpoint, with a statistical power that was most often below 20 % according to a posteriori computations [136]. Despite this limitation, PRT significantly improved balance in roughly half of these studies. In addition, the effect was most prominent in the studies that (1) had a higher statistical power, (2) used a higher intensity training program, (3) focused on frail elderly people, and (4) used a dynamic rather than a static balance test [136]. This latter part could be expected since dynamic balance (the ability to execute a response following a balance perturbation) is more demanding in terms of muscle power than static balance. Other studies published since 2008 have provided

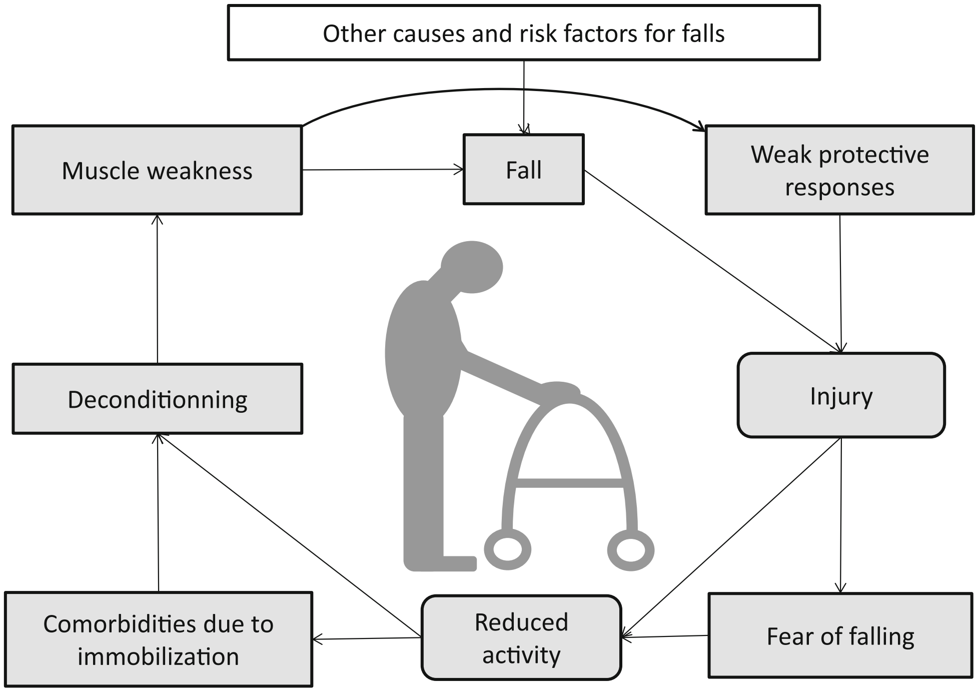


**Fig. 3** Downward spiral of falls and related injuries. Older people have an increased fall frequency, high susceptibility to injury, and slow recovery. These characteristics contribute to a vicious circle through which injurious fall induce deconditioning and predispose to further falls and associated harm. In addition, fear of falling may arise at various levels of the disablement process and reduce physical activity even in the absence of previous falls or fall injuries

somewhat heterogeneous results, but the findings of the majority are consistent with those from earlier studies [137–141]. In addition to these effects on various measures of balance, biomechanical studies with older adults have shown that PRT reduces slip propensity and severity [142] and improves the ability to recover from a leaning position [143].

### Effects of PRT on the Rate of Falls

More than 150 clinical trials have evaluated exercise training in the prevention of falls [144]. While overall, exercise reduces the risk of falls, the vast majority of trials have included combinations of various exercise types, including not only muscle strengthening procedures but also balance, endurance, and flexibility training. The systematic review by Sherrington et al. concluded that balance training was the most essential component for efficacious exercise fall prevention [145]. This likely indicates that balance training generalizes readily to activities of living skills required by older people. However, the systematic review was based on brief descriptions of exercise content of published trials, and it proved difficult to dissect out balance training from muscle strengthening or other types of exercise in many studies. Eight published studies have investigated the effects of PRT alone (i.e., without any other intervention such as balance training) on the risk of falls in samples with average age of at least 75 years [146–153]. This list excludes studies that have focused on specific diseases (cardiac cachexia, COPD, diabetes, and cancer cachexia) which may not respond homogeneously to such intervention. These trials testing PRT alone were underpowered for falls as an outcome, but have showed trends for a decrease in fall rate in the PRT arm versus control, despite the fact that none of these trials specifically targeted weak subjects. In addition to improving muscle strength and power, PRT has demonstrated benefits for several physiological systems, as well as for mental health [154] and cognition (especially executive functioning) [155]. Such benefits may constitute ancillary mechanisms for preventing falls and improving mobility in older people.

### Effects of PRT on the Rate of Fall-Related Injuries

No studies have published findings on the effects of PRT alone on the risk of fall-related injuries. However, a meta-analysis of fall prevention trials using various combinations of exercise showed stronger efficacy on the most severe forms of injuries compared to less severe forms [156]. Specifically, in this analysis, the authors concluded that exercise reduced the risk of all injurious falls by 37 % and of falls requiring medical care by 30 %, compared with 43 % for severe injuries and 61 % for fractures [156]. These results suggest that exercise training reduced not only the risk of falling (by improving dynamic balance) but also the risk of a resulting injury when falling (by improving the efficacy of protective responses). Similarly, with a treatment strategy based upon an increase in muscle power, improving both dynamic balance and protective responses would be expected to have a stronger preventive effect toward more severe falls.

## Unmet Need in Fall Prevention: Exercise Training with Muscle Strengthening is One of the Main Pillars of Fall Prevention but it is Rarely Implemented in Routine Practice Due to Multiple Challenges Inherent to the Target Population

Despite the multifactorial nature of falls, the evidence summarized in the first parts of this paper supports the hypothesis that increasing muscle strength and power should reduce the risk of falls and related injuries.

Although a robust demonstration of this concept will only come from a dedicated, appropriately sized, clinical trial, this evidence is considered strong enough that the current standard of care to prevent falls and related injuries in older people at high risk for falls relies essentially on (1) exercise training intended to increase lower limb muscle strength/power and to improve balance, both of which are frequently impaired in elderly fallers, and (2) customized interventions intended to correct individual risk factors according to each patient's needs: improving vision, decreasing the number of psychotropic drugs, treating orthostatic hypotension, removing home hazards, etc. [157].

Despite the efficacy of these interventions, falls and related injuries remain a major health issue for elderly people, mainly for three reasons. First, although clinical practice varies across countries, use of physical rehabilitation or enrollment in a fall prevention program is rare, even after an ER admission for a fall [158–160]. Multiple reasons have been identified for the very low uptake of fall prevention strategies especially in terms of exercise training: presence of mobility impairment, transportation challenges, recurrent relocations, painful musculoskeletal conditions, unstable comorbidities, denial of fall risk, etc. [161–164]. Second, exercise (group or home-based exercise programs) reduces the rate of falls and the risk of falling by approximately 15–30 % according to published studies [144], which means that 70–85 % of the falls still occur despite such interventions. Third, the long-term sustainability of the benefits of exercise training is unknown.

Some alternatives to exercise training have been suggested as strategies for preventing falls. These include whole body vibration training, electrical stimulation of critical muscle groups, perturbation training, and nutritional supplementation. Systematic review evidence indicates that the evidence for whole body vibration therapy in preventing falls is inconclusive [165]. However, a recent large RCT found low-magnitude high-frequency vibration was effective in improving muscle strength and balance and reducing falls over an 18-month period [166]. There is only preliminary evidence for electrical stimulation as a fall prevention strategy in older people, with pilot studies indicating electrical stimulation can improve measures of muscle mass and mobility [167]. Several small trials have examined the effects of perturbation training on balance recovery and two large trials have demonstrated single session perturbation (slip or trip recovery) training have lasting benefits for fall prevention [168]. Finally, large epidemiological trials have revealed poor nutritional status is a risk factor for immobility and falls [169, 170], but systematic review evidence from three studies indicates nutritional supplementation as a single fall prevention strategy does not reduce the risk of falls [144]. The above strategies present some potential opportunities for fall prevention, but each has limitations regarding contraindications, acceptability, accessibility and reach.

Therefore, a pharmacologic treatment for increasing muscle strength and power may fulfill a significant unmet need in the care of the elderly, by reducing the rate and severity of falls as well as their devastating consequences. A number of molecules are being developed that have the potential to increase muscle strength and power. These include androgens, SARMs, and drugs targeting the myostatin pathway.

## Drugs that are Currently Being Developed to Increase Muscle Mass and Strength Could be Tested for Reducing the Risk of Fall-Related Injuries

Testosterone has been shown to increase muscle mass and strength in several clinical trials, including in older men with mobility limitations [171]. However, for safety reasons, its use is likely to remain confined to men with testosterone deficiency. Several selective androgen receptor modulators (SARMs) are being developed to increase muscle strength with the hope that they would not have the same safety liabilities as testosterone. The most advanced molecule in this field is enobosarm, for which there is published phase 2 data showing a statistically significant increase in stair climbing power in a population of patients with cancer [172]. However, this efficacy was not confirmed in phase 3, and it is not yet known whether this latter result was due to the molecule itself or to the fact that the high number of sites in phase 3 led to unacceptably high variability of the outcome measure [173]. Other SARMS have entered clinical stages of development [174]. Finally, a number of drugs are being developed that target the myostatin pathway. These include several anti-myostatin antibodies, one of which has been shown to improve power intensive measures of physical function in 102 elderly weak fallers compared with 99 patients receiving placebo [175], and an antibody directed to the receptor for myostatin/activin which has been shown to increase 6 min walking distance in 11 patients with inclusion body myositis versus 3 placebo patients [176].

While all these molecules may have the potential to reduce the risk of falls and related injuries, they would have to fulfill two pre-requisites: (1) to have a clean safety profile since the target population is large and has multiple comorbidities, and (2) to increase muscle power sufficiently for the effect on falls to be clinically meaningful and to be detected in a reasonably sized clinical trial.

## What Could Make Muscle Strengthening Fail to Reduce the Risk of Falls and Related Injuries?

### Falls are Too Multifactorial

Falls are so multifactorial in nature that the effect size of a muscle drug (single intervention) might be too small to be clinically meaningful and/or to be detectable in a clinical trial. For instance, it is unclear whether increasing muscle power would reduce the risk of falling in a severely demented older person whose falls are driven by hazardous behaviors. Therefore, for such a pharmacologic treatment to work on falls, the population should be carefully tailored to the expected mechanism of action. This means not only including older people with muscle weakness, but also excluding patients with major confounders, i.e., those with major causes for falls independent of muscle weakness (end stage Parkinson disease, dementia, etc.). The feasibility of recruiting such a population has been demonstrated by a clinical trial testing an anti-myostatin monoclonal antibody versus placebo in older weak fallers [175].

Another design feature that could help reduce the influence of confounders is the choice of the outcome measure for falls. The Kellogg International Working Group on the Prevention of Falls in the Elderly defined a fall as "unintentionally coming to the ground or some lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure" [177]. By excluding falls due to major intrinsic events or overwhelming environmental hazards, it allows to focus on the type of falls that is amenable to interventions such as those improving muscle power and dynamic balance. The PROFANE definition [178], on the other hand, includes falls from all causes, and is therefore more appropriate for other situations such as studies that are not focused on a specific mechanism of falling, or when details of falls are unrecorded (routine surveillance data/accident records), or where a high proportion of subjects cannot provide reliable information about their falls (i.e., those with delirium and cognitive impairment).

Also single interventions, and in particular exercise interventions, have been shown to be as effective as multifactorial interventions in preventing falls in older people [179]. Further, this would not be the first multifactorial event that could be prevented by a drug targeting only one out of multiple risk factors. Another classical example is the reduction of risk of major cardiovascular events (MACE) with cholesterol lowering drugs including statins. Risk factors for MACE include not only high LDL cholesterol but also low HDL cholesterol, high blood pressure, smoking, heredity, diabetes, high C-reactive protein, etc., and many patients have multiple risk factors. Despite this multifactorial nature, it has been possible to demonstrate repeatedly that statins decrease the risk of MACE, both in secondary and in primary prevention, and without even excluding participants with other major MACE risk factors independent of cholesterol levels [180, 181].

### Increasing Muscle Strength and/or Power May Increase the Risk of Falling

It could be speculated that a higher muscle power could increase physical activity, which in turn could increase older people's exposure to the risk of falling. While this possibility cannot be ruled out without an appropriately sized clinical trial, it is important to note that the first assumption enabling this hypothesis is not demonstrated: as of today, we are not aware of any published data showing that an increase in muscle strength or power could result in increased physical activity. In fact, some data suggest the opposite: a clinical trial using progressive resistance exercise led to significant improvements in physical function without any increase in physical activity in functionally limited older adults [182].

### Expected Differential Effects on Muscle of PRT Compared to a Drug Increasing Muscle Strength and/or Power

One could fear that a drug increasing muscle mass does not have all the benefits of PRT which is thought to not only increase muscle mass and power but also train a functional skill. It appears that several drugs increasing muscle mass do improve measures of lower limb physical function such as stair climbing performance in the absence of any systematic exercise training [171, 175]. In addition, a drug that is to be administered systemically may increase muscle power in all muscle groups as opposed to PRT which is not feasible in routine for more than a few muscles. Published studies suggest that muscles involved in balance recovery and protective responses are numerous and include not only lower limb muscles such as the quadriceps, hamstring, gluteal medius, gastrocnemius, and ankle dorsiflexors and plantarflexors, but also multiple trunk and upper limb muscles [45, 86, 183]. This difference represents a potential advantage for a muscle drug over PRT for the purpose of preventing falls and related injuries. Another hypothetical issue is that the positive effect of exercise on the risk of falls might result partially from a positive effect on bone strength (through increased loading for instance), which would not necessarily be obtained with a drug increasing muscle power. As of today, the evidence available does not clearly support this hypothesis [184].

### Should Exercise Training and/or Nutritional Supplementation be Expected to Work Synergistically with a Drug Increasing Muscle Mass and Power?

Older malnourished people might not have the nutrients necessary to accrue muscle mass hence benefit optimally from a muscle anabolic treatment. Therefore, in such a population, a protein-enriched diet may enhance the effect of such a drug and result in synergy. Whether this would be also true for older people with a normal nutritional status is debatable. While an additive effect is likely, the authors are not aware of published evidence supporting true synergy (i.e., a total muscle mass/power increase that is superior to the sum of the increases induced by the drug and the protein enrichment.).

The scarce information published about the combination of exercise with a muscle anabolic treatment versus none or either of these two does not suggest synergistic effects either [185, 186]. However, this absence of published evidence does not definitely exclude the possibility of a synergy. The trial by Bhasin et al. [185] tested supra-physiologic doses of testosterone versus placebo with or without resistance exercise training in healthy young men. It reported additive effects on muscle mass as well as muscle strength, but did not involve really functional measures such as climbing stairs or rising from a chair. The trial by Hildreth et al. [186] tested testosterone supplementation versus placebo with or without resistance exercise in older men with low-normal testosterone; this one failed to detect any positive effects of testosterone on strength or function (maybe due to the small sample size), so the absence of observed synergy should not necessarily be taken at face value here.

Exercise training is very complex and costly to standardize in late phase drug development, so the decision to include it in a drug trial should rely on solid evidence. In addition, drug developers are facing conflicting needs from various stakeholders including prescribers, regulators, and payers. Comparing an investigational drug (head to head) to standard of care (exercise training) may not be acceptable for regulatory approval due to the impossibility of a fully blinded design. Therefore, and in the absence of any drug approved for fall prevention in older weak fallers, a comparison to placebo is the most logical choice. Should this comparison be performed on background standard of care, i.e., in patients who all perform exercise training? In this case, the trial would not be representative of routine practice since this high risk population hardly performs any fall prevention exercises in the real world. On the other hand, performing such trials on background usual care (i.e., allowing investigators to choose how they want to prevent falls in their patients) may not be acceptable to the stakeholders who want to know whether the investigational drug adds anything to exercise. The ideal solution would be to test both designs, as long as resources are available to do so.

## Conclusion

In conclusion, the considerable evidence supporting the hypothesis that a muscle strengthening approach could reduce the risk of fall-related injuries contrasts with the absence of formal demonstration of such an effect.

The ongoing development of drugs expected to increase muscle power offers a new opportunity to address this major unmet need. The intent here is not to replace exercise training with drugs but rather to offer a pharmacologic alternative to older people who are at high risk of fall-related injuries and (1) who cannot perform resistance exercise training due to musculoskeletal pain or other reasons, or (2) who continue falling despite standard of care including resistance training. Potentially, a pharmaceutical could also be offered in combination with balance training or task specific strength training in weak older people at increased fall risk.

Because of the multifactorial nature of falls, the intervention would need to be targeted to the population that would benefit from the posited mechanism of action, i.e., weak patients, excluding those with major causes for falls independent of muscle weakness. Provided such a targeted strategy was followed, the central role of muscle power in dynamic balance and protective responses suggests that a muscle anabolic may indeed address this major unmet need.

**Acknowledgments** The authors would like to thank Kathryn Krueger for critical review of the manuscript.

#### Compliance with Ethical Standards

**Conflict of Interest** Olivier Benichou is full time employee, and owns stocks, of Eli Lilly and company. Stephen R. Lord reports consulting fees from Eli Lilly, outside the submitted work.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References


1. Berry SD, Miller RR (2008) Falls: epidemiology, pathophysiology, and relationship to fracture. Curr Osteoporos Rep 6(4):149–154
2. Rubenstein LZ (2006) Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing 35 Suppl 2:ii37–ii41
3. Kannus P, Sievänen H, Palvanen M, Järvinen T, Parkkari J (2005) Prevention of falls and consequent injuries in elderly people. Lancet 366(9500):1885–1893
4. Peeters G, van Schoor NM, Lips P (2009) Fall risk: the clinical relevance of falls and how to integrate fall risk with fracture risk. Best Pract Res Clin Rheumatol 23(6):797–804
5. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS) [online]. Accessed 11 Sept 2015
6. Owens PL, Russo CA, Spector W, Mutter R. Emergency Department visits for injurious falls among the elderly, 2006: Statistical Brief #80. 2009 Oct. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Health Care Policy and Research (US); 2006 Feb. http://www.ncbi.nlm.nih.gov/books/NBK53603. Accessed 11 Sept 2015
7. Korhonen N, Niemi S, Parkkari J, Sievänen H, Kannus P (2013) Incidence of fall-related traumatic brain injuries among older Finnish adults between 1970 and 2011. JAMA 309(18): 1891–1892
8. Center for Disease Control and Prevention. Older Adult Falls: Get the Facts. http://www.cdc.gov/HomeandRecreationalSafety/Falls/adultfalls.html. Accessed 11 Sept 2015
9. Lachman ME, Howland J, Tennstedt S, Jette A, Assmann S, Peterson EW (1998) Fear of falling and activity restriction: the survey of activities and fear of falling in the elderly (SAFE). J Gerontol B Psychol Sci Soc Sci 53(1):P43–P50
10. Petrella RJ, Payne M, Myers A, Overend T, Chesworth B (2000) Physical function and fear of falling after hip fracture rehabilitation in the elderly. Am J Phys Med Rehabil 79(2):154–160
11. Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE, Quine S (2000) Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ 320(7231):341–346
12. Li F, Fisher KJ, Harmer P, McAuley E, Wilson NL (2003) Fear of falling in elderly persons: association with falls, functional ability, and quality of life. J Gerontol B Psychol Sci Soc Sci 58(5):P283–P290
13. Tinetti ME, Powell L (1993) Fear of falling and low self-efficacy: a case of dependence in elderly persons. J Gerontol 48 Spec No:35–38
14. Tinetti ME, Williams CS (1997) Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med 337(18):1279–1284
15. Järvinen TL, Sievänen H, Khan KM, Heinonen A, Kannus P (2008) Shifting the focus in fracture prevention from osteoporosis to falls. BMJ 336(7636):124–126
16. Briot K, Cortet B, Thomas T, Audran M, Blain H, Breuil V, Chapuis L, Chapurlat R, Fardellone P, Feron JM, Gauvain JB, Guggenbuhl P, Kolta S, Lespessailles E, Letombe B, Marcelli C, Orcel P, Seret P, Trémollières F, Roux C (2012) 2012 update of French guidelines for the pharmacological treatment of postmenopausal osteoporosis. Joint Bone Spine 79(3):304–313
17. Hiligsmann M, Salas M, Hughes DA, Manias E, Gwadry-Sridhar FH, Linck P, Cowell W (2013) Interventions to improve osteoporosis medication adherence and persistence: a systematic review and literature appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group. Osteoporos Int 24(12):2907–2918
18. Compston JE, Seeman E (2006) Compliance with osteoporosis therapy is the weakest link. Lancet 368(9540):973–974
19. Melton LJ 3rd, Thamer M, Ray NF, Chan JK, Chesnut CH 3rd, Einhorn TA, Johnston CC, Raisz LG, Silverman SL, Siris ES (1997) Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. J Bone Miner Res 12(1):16–23
20. Järvinen TL, Michaëlsson K, Aspenberg P, Sievänen H (2015) Osteoporosis: the emperor has no clothes. J Intern Med 277(6):662–673
21. Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS et al (2003) BMD at multiple sites and risk of fracture of multiple types: long-term results from the study of osteoporotic fractures. J Bone Miner Res 18:1947–1954
22. Zhu K, Devine A, Lewis JR, Dhaliwal SS, Prince RL (2011) Timed up and go' test and bone mineral density measurement for fracture prediction. Arch Intern Med 171(18):1655–1661
23. Cummings SR, Nevitt MC (1994) Non-skeletal determinants of fractures: the potential importance of the mechanics of falls. Study of Osteoporotic Fractures Research Group. Osteoporos Int 4(Suppl 1):67–70
24. Norton R, Campbell AJ, Lee-Joe T, Robinson E, Butler M (1997) Circumstances of falls resulting in hip fractures among older people. J Am Geriatr Soc 45(9):1108–1112
25. Palvanen M, Kannus P, Parkkari J, Pitkäjärvi T, Pasanen M, Vuori I, Järvinen M (2000) The injury mechanisms of osteoporotic upper extremity fractures among older adults: a controlled study of 287 consecutive patients and their 108 controls. Osteoporos Int 11(10):822–831
26. Nevitt MC, Ettinger B, Black DM et al (1998) The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 128:793–800
27. Cooper C, Atkinson EJ, O'Fallon WM et al (1992) Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. J Bone Miner Res 7:221–227
28. Fink HA, Milavetz DL, Palermo L et al (2005) What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? J Bone Min Res 20:1216–1222
29. Ettinger B, Black DM, Mitlak BH et al (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results froma 3-year randomized clinical trial. Multiple outcomes of raloxifene evaluation (MORE) investigators. JAMA 282:637–645
30. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB (2009) Incidence and mortality of hip fractures in the United States. JAMA 302(14):1573–1579
31. Carpintero P, Caeiro JR, Carpintero R, Morales A, Silva S, Mesa M (2014) Complications of hip fractures: a review. World J Orthop 5(4):402–411
32. Mundi S, Pindiprolu B, Simunovic N, Bhandari M (2014) Similar mortality rates in hip fracture patients over the past 31 years. Acta Orthop 85(1):54–59
33. Braithwaite RS, Col NF, Wong JB (2003) Estimating hip fracture morbidity, mortality and costs. J Am Geriatr Soc 51(3):364–370
34. Delmas PD, Marin F, Marcus R, Misurski DA, Mitlak BH (2007) Beyond hip: importance of other nonspinal fractures. Am J Med 120(5):381–387

35. Chen JS, Simpson JM, March LM, Cameron ID, Cumming RG, Lord SR, Seibel MJ, Sambrook PN (2008) Risk factors for fracture following a fall among older people in residential care facilities in Australia. J Am Geriatr Soc 56(11):2020–2026
36. Courtney AC, Wachtel EF, Myers ER, Hayes WC (1995) Age-related reductions in the strength of the femur tested in a fall-loading configuration. J Bone Joint Surg Am 77(3):387–395
37. Robinovitch SN, Hsiao ET, Sandler R, Cortez J, Liu Q, Paiement GD (2000) Prevention of falls and fall-related fractures through biomechanics. Exerc Sport Sci Rev 28(2):74–79
38. Hayes WC, Myers ER, Morris IN, Gerhart TN, Yeti HS, Lipsitz LA (1993) Impact near the hip dominates fracture risk in elderly nursing home residents who fall. Calcif Tissue Int 52:192–198
39. Hayes WC, Piazza SJ, Zysset PK (1991) Biomechanics of fracture risk prediction of the hip and spine by quantitative computed tomography. Radiol Clin North Am 29:1–18
40. Deandrea S, Bravi F, Turati F, Lucenteforte E, La Vecchia C, Negri E (2013) Risk factors for falls in older people in nursing homes and hospitals. A systematic review and meta-analysis. Arch Gerontol Geriatr 56(3):407–415
41. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E (2010) Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. Epidemiology 21(5):658–668
42. Ambrose AF, Paul G, Hausdorff JM (2013) Risk factors for falls among older adults: a review of the literature. Maturitas 75(1):51–61
43. Moreland JD, Richardson JA, Goldsmith CH, Clase CM (2004) Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 52(7):1121–1129
44. Ward RE, Leveille SG, Beauchamp MK, Travison T, Alexander N, Jette AM, Bean JF (2015) Functional performance as a predictor of injurious falls in older adults. J Am Geriatr Soc 63(2):315–320
45. Horlings CG, van Engelen BG, Allum JH, Bloem BR (2008) A weak balance: the contribution of muscle weakness to postural instability and falls. Nat Clin Pract Neurol 4(9):504–515
46. Yau DT, Chung RC, Pang MY (2013) Knee muscle strength and visual acuity are the most important modifiable predictors of falls in patients after hip fracture surgery: a prospective study. Calcif Tissue Int 92(3):287–295
47. de Rekeneire N, Visser M, Peila R, Nevitt MC, Cauley JA, Tylavsky FA, Simonsick EM, Harris TB (2003) Is a fall just a fall: correlates of falling in healthy older persons. The Health, Aging and Body Composition Study. J Am Geriatr Soc 51(6):841–846
48. Chan BK, Marshall LM, Winters KM, Faulkner KA, Schwartz AV, Orwoll ES (2007) Incident fall risk and physical activity and physical performance among older men: the Osteoporotic Fractures in Men Study. Am J Epidemiol 165(6):696–703
49. Tiedemann A, Shimada H, Sherrington C, Murray S, Lord S (2008) The comparative ability of eight functional mobility tests for predicting falls in community-dwelling older people. Age Ageing 37(4):430–435
50. Perry MC, Carville SF, Smith IC, Rutherford OM, Newham DJ (2007) Strength, power output and symmetry of leg muscles: effect of age and history of falling. Eur J Appl Physiol 100(5):553–561
51. Scott D, Stuart AL, Kay D, Ebeling PR, Nicholson G, Sanders KM (2014) Investigating the predictive ability of gait speed and quadriceps strength for incident falls in community-dwelling older women at high risk of fracture. Arch Gerontol Geriatr. 58(3):308–313
52. Karinkanta S, Heinonen A, Sievanen H, Uusi-Rasi K, Kannus P (2005) Factors predicting dynamic balance and quality of life in home-dwelling elderly women. Gerontology 51(2):116–121
53. Hasselgren L, Olsson LL, Nyberg L (2011) Is leg muscle strength correlated with functional balance and mobility among inpatients in geriatric rehabilitation? Arch Gerontol Geriatr 52(3):e220–e225
54. Tinetti ME (1987) Factors associated with serious injury during falls by ambulatory nursing home residents. J Am Geriatr Soc 35(7):644–648
55. Nevitt MC, Cummings SR, Hudes ES (1991) Risk factors for injurious falls: a prospective study. J Gerontol 46(5):M164–M170
56. Lord SR, Ward JA, Williams P, Anstey KJ (1994) Physiological factors associated with falls in older community-dwelling women. J Am Geriatr Soc 42(10):1110–1117
57. Lord SR, Sambrook PN, Gilbert C, Kelly PJ, Nguyen T, Webster IW, Eisman JA (1994) Postural stability, falls and fractures in the elderly: results from the Dubbo Osteoporosis Epidemiology Study. Med J Aust 160(11):684–685, 688–691
58. Nguyen ND, Pongchaiyakul C, Center JR, Eisman JA, Nguyen TV (2005) Identification of high-risk individuals for hip fracture: a 14-year prospective study. J Bone Miner Res 20(11):1921–1928 **Epub 2005 May 31**
59. Lloyd BD, Williamson DA, Singh NA, Hansen RD, Diamond TH, Finnegan TP, Allen BJ, Grady JN, Stavrinos TM, Smith EU, Diwan AD, Fiatarone Singh MA (2009) Recurrent and injurious falls in the year following hip fracture: a prospective study of incidence and risk factors from the Sarcopenia and Hip Fracture study. J Gerontol A Biol Sci Med Sci 64(5):599–609
60. Shigematsu R, Rantanen T, Saari P, Sakari-Rantala R, Kauppinen M, Sipilä S, Heikkinen E (2006) Motor speed and lower extremity strength as predictors of fall-related bone fractures in elderly individuals. Aging Clin Exp Res 18(4):320–324
61. Albrand G, Munoz F, Sornay-Rendu E, DuBoeuf F, Delmas PD (2003) Independent predictors of all osteoporosis-related fractures in healthy postmenopausal women: the OFELY study. Bone 32(1):78–85
62. Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, Eisman J (1993) Prediction of osteoporotic fractures by postural instability and bone density. BMJ 307(6912):1111–1115
63. Cawthon PM, Fullman RL, Marshall L, Mackey DC, Fink HA, Cauley JA, Cummings SR, Orwoll ES, Ensrud KE (2008) Osteoporotic Fractures in Men (MrOS) Research Group. Physical performance and risk of hip fractures in older men. J Bone Miner Res 23(7):1037–1044
64. Bischoff-Ferrari HA, Orav JE, Kanis JA, Rizzoli R, Schlögl M, Staehelin HB, Willett WC, Dawson-Hughes B (2015) Comparative performance of current definitions of sarcopenia against the prospective incidence of falls among community-dwelling seniors age 65 and older. Osteoporos Int 26(12):2793–2802
65. Scott D, Hayes A, Sanders KM, Aitken D, Ebeling PR, Jones G (2014) Operational definitions of sarcopenia and their associations with 5-year changes in falls risk in community-dwelling middle-aged and older adults. Osteoporos Int 25(1):187–193
66. Lang T, Cauley JA, Tylavsky F, Bauer D, Cummings S, Harris TB, Health ABC (2010) Study. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. J Bone Miner Res 25(3):513–519
67. Chalhoub D et al (2015) Osteoporotic Fractures in Men Study Research Group. Risk of nonspine fractures in older adults with sarcopenia, low bone mass, or both. J Am Geriatr Soc 63(9):1733–1740
68. Malkov S, Health ABC Study et al (2015) Hip fractures risk in older men and women associated with DXA-derived measures of thigh subcutaneous fat thickness, cross-sectional muscle area, and muscle density. J Bone Miner Res 30(8):1414–1421

69. Lockhart TE, Smith JL, Woldstad JC (2005) Effects of aging on the biomechanics of slips and falls. Hum Factors 47(4):708–729
70. Corriveau H, Hébert R, Raîche M, Dubois MF, Prince F (2004) Postural stability in the elderly: empirical confirmation of a theoretical model. Arch Gerontol Geriatr 39(2):163–177
71. Pijnappels M, Reeves ND, Maganaris CN, van Dieën JH (2008) Tripping without falling; lower limb strength, a limitation for balance recovery and a target for training in the elderly. J Electromyogr Kinesiol 18(2):188–196
72. Barrett RS, Mills PM, Begg RK (2010) A systematic review of the effect of ageing and falls history on minimum foot clearance characteristics during level walking. Gait Posture 32(4):429–435
73. Hiscock A, Dewar L, Parton M, Machado P, Hanna M, Ramdharry G (2014) Frequency and circumstances of falls in people with inclusion body myositis: a questionnaire survey to explore falls management and physiotherapy provision. Physiotherapy 100(1):61–65
74. Aprile I, Padua L, Iosa M, Gilardi A, Bordieri C, Frusciante R, Russo G, Erra C, De Santis F, Ricci E (2012) Balance and walking in facioscapulohumeral muscular dystrophy: multiperspective assessment. Eur J Phys Rehabil Med 48(3):393–402
75. Horlings CG, Munneke M, Bickerstaffe A, Laverman L, Allum JH, Padberg GW, Bloem BR, van Engelen BG (2009) Epidemiology and pathophysiology of falls in facioscapulohumeral disease. J Neurol Neurosurg Psychiatry 80(12):1357–1363
76. Wiles CM, Busse ME, Sampson CM, Rogers MT, Fenton-May J, van Deursen R (2006) Falls and stumbles in myotonic dystrophy. J Neurol Neurosurg Psychiatry 77(3):393–396
77. Hammarén E, Kjellby-Wendt G, Lindberg C (2015) Muscle force, balance and falls in muscular impaired individuals with myotonic dystrophy type 1: a five-year prospective cohort study. Neuromuscul Disord 25(2):141–148
78. Pai YC, Yang F, Wening JD, Pavol MJ (2006) Mechanisms of limb collapse following a slip among young and older adults. J Biomech 39(12):2194–2204
79. Hsiao ET, Robinovitch SN (1998) Common protective movements govern unexpected falls from standing height. J Biomech 31(1):1–9
80. van Dieën JH, Spanjaard M, Konemann R, Bron L, Pijnappels M (2007) Balance control in stepping down expected and unexpected level changes. J Biomech 40(16):3641–3649
81. Mackey DC, Robinovitch SN (2006) Mechanisms underlying age-related differences in ability to recover balance with the ankle strategy. Gait Posture 23(1):59–68
82. Carbonneau E, Smeesters C (2014) Effects of age and lean direction on the threshold of single-step balance recovery in younger, middle-aged and older adults. Gait Posture 39(1):365–371
83. Matrangola SL, Madigan ML (2009) Relative effects of weight loss and strength training on balance recovery. Med Sci Sports Exerc 41(7):1488–1493
84. Graham DF, Carty CP, Lloyd DG, Barrett RS (2015) Biomechanical predictors of maximal balance recovery performance amongst community-dwelling older adults. Exp Gerontol 66:39–46
85. Pijnappels M, van der Burg PJ, Reeves ND, van Dieën JH (2008) Identification of elderly fallers by muscle strength measures. Eur J Appl Physiol 102(5):585–592
86. Granacher U, Gollhofer A, Hortobágyi T, Kressig RW, Muehlbauer T (2013) The importance of trunk muscle strength for balance, functional performance, and fall prevention in seniors: a systematic review. Sports Med 43(7):627–641
87. Roos PE, McGuigan MP, Kerwin DG, Trewartha G (2008) The role of arm movement in early trip recovery in younger and older adults. Gait Posture 27(2):352–356
88. Milosevic M, McConville KM, Masani K (2011) Arm movement improves performance in clinical balance and mobility tests. Gait Posture 33(3):507–509
89. Pijnappels M, Kingma I, Wezenberg D, Reurink G, van Dieën JH (2010) Armed against falls: the contribution of arm movements to balance recovery after tripping. Exp Brain Res 201(4):689–699
90. Cheng KB, Huang YC, Kuo SY (2014) Effect of arm swing on single-step balance recovery. Hum Mov Sci 38:173–184
91. Grin L, Frank J, Allum JH (2007) The effect of voluntary arm abduction on balance recovery following multidirectional stance perturbations. Exp Brain Res 178(1):62–78
92. Allum JH, Carpenter MG, Honegger F, Adkin AL, Bloem BR (2002) Age-dependent variations in the directional sensitivity of balance corrections and compensatory arm movements in man. J Physiol 542(Pt 2):643–663
93. Maki BE, McIlroy WE (2006) Control of rapid limb movements for balance recovery: age-related changes and implications for fall prevention. Age Ageing 35 Suppl 2:ii12–ii18
94. Reid KF, Fielding RA (2012) Skeletal muscle power: a critical determinant of physical functioning in older adults. Exerc Sport Sci Rev 40(1):4–12
95. Bean JF, Leveille SG, Kiely DK, Bandinelli S, Guralnik JM, Ferrucci L (2003) A comparison of leg power and leg strength within the InCHIANTI study: which influences mobility more? J Gerontol A Biol Sci Med Sci 58(8):728–733
96. Mayson DJ, Kiely DK, LaRose SI, Bean JF (2008) Leg strength or velocity of movement: which is more influential on the balance of mobility limited elders? Am J Phys Med Rehabil 87(12):969–976
97. Thelen DG, Schultz AB, Alexander NB, Ashton-Miller JA (1996) Effects of age on rapid ankle torque development. J Gerontol A Biol Sci Med Sci 51(5):M226–M232
98. Frontera WR, Hughes VA, Lutz KJ, Evans WJ (1991) A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. J Appl Physiol (1985) 71(2):644–650
99. Izquierdo M, Aguado X, Gonzalez R, López JL, Häkkinen K (1999) Maximal and explosive force production capacity and balance performance in men of different ages. Eur J Appl Physiol Occup Physiol 79(3):260–267
100. Häkkinen K, Kraemer WJ, Kallinen M, Linnamo V, Pastinen UM, Newton RU (1996) Bilateral and unilateral neuromuscular function and muscle cross-sectional area in middle-aged and elderly men and women. J Gerontol A Biol Sci Med Sci 51(1):B21–B29
101. Kostka T (2005) Quadriceps maximal power and optimal shortening velocity in 335 men aged 23–88 years. Eur J Appl Physiol 95:140–145
102. Looker AC, Wang CY (2015) Prevalence of reduced muscle strength in older U.S. adults: United States, 2011–2012. NCHS Data Brief (179):1–8
103. Manini TM, Hong SL, Clark BC (2013) Aging and muscle: a neuron's perspective. Curr Opin Clin Nutr Metab Care 16(1):21–26
104. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M (2011) Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 12(4):249–256
105. Cohen S, Nathan JA, Goldberg AL (2014) Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov 14(1):58–74

106. Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB (2010) Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int 21(4):543–559
107. McNeil CJ, Vandervoort AA, Rice CL (2007) Peripheral impairments cause a progressive age-related loss of strength and velocity-dependent power in the dorsiflexors. J Appl Physiol (1985) 102(5):1962–1968
108. Van Roie E, Verschueren SM, Boonen S, Bogaerts A, Kennis E, Coudyzer W, Delecluse C (2011) Force-velocity characteristics of the knee extensors: an indication of the risk for physical frailty in elderly women. Arch Phys Med Rehabil 92(11):1827–1832
109. Lanza IR, Towse TF, Caldwell GE, Wigmore DM, Kent-Braun JA (2003) Effects of age on human muscle torque, velocity, and power in two muscle groups. J Appl Physiol (1985) 95(6):2361–2369
110. Luukinen H, Koski K, Laippala P, Kivela SL (1997) Factors predicting fractures during falling impacts among home-dwelling older adults. J Am Geriatr Soc 45(11):1302–1309
111. Rosengren BE, Ribom EL, Nilsson JÅ, Mallmin H, Ljunggren O, Ohlsson C, Mellström D, Lorentzon M, Stefanick M, Lapidus J, Leung PC, Kwok A, Barrett-Connor E, Orwoll E, Karlsson MK (2012) Inferior physical performance test results of 10,998 men in the MrOS Study is associated with high fracture risk. Age Ageing 41(3):339–344
112. Nevitt MC, Cummings SR (1993) Type of fall and risk of hip and wrist fractures: the study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc 41(11):1226–1234
113. Robinovitch SN, Inkster L, Maurer J, Warnick B (2003) Strategies for avoiding hip impact during sideways falls. J Bone Miner Res 18(7):1267–1273
114. Sabick MB, Hay JG, Goel VK, Banks SA (1999) Active responses decrease impact forces at the hip and shoulder in falls to the side. J Biomech 32(9):993–998
115. DeGoede KM, Ashton-Miller JA, Schultz AB (2003) Fall-related upper body injuries in the older adult: a review of the biomechanical issues. J Biomech 36(7):1043–1053
116. DeGoede KM, Ashton-Miller JA (2003) Biomechanical simulations of forward fall arrests: effects of upper extremity arrest strategy, gender and aging-related declines in muscle strength. J Biomech 36(3):413–420
117. Feldman F, Robinovitch SN (2007) Reducing hip fracture risk during sideways falls: evidence in young adults of the protective effects of impact to the hands and stepping. J Biomech 40(12):2612–2618
118. Schwartz AV, Kelsey JL, Sidney S, Grisso JA (1998) Characteristics of falls and risk of hip fracture in elderly men. Osteoporos Int 8(3):240–246
119. Sandler R, Robinovitch S (2001) An analysis of the effect of lower extremity strength on impact severity during a backward fall. J Biomech Eng 123(6):590–598
120. Sterling DA, O'Connor JA, Bonadies J (2001) Geriatric falls: injury severity is high and disproportionate to mechanism. J Trauma 50(1):116–119
121. Vellas BJ, Wayne SJ, Romero LJ, Baumgartner RN, Garry PJ (1997) Fear of falling and restriction of mobility in elderly fallers. Age Ageing 26(3):189–193
122. Myers AM, Powell LE, Maki BE, Holliday PJ, Brawley LR, Sherk W (1996) Psychological indicators of balance confidence: relationship to actual and perceived abilities. J Gerontol A Biol Sci Med Sci 51(1):M37–M43
123. Trombetti A, Reid KF, Hars M, Herrmann FR, Pasha E, Phillips EM, Fielding RA (2015) Age-associated declines in muscle mass, strength, power, and physical performance: impact on fear of falling and quality of life. Osteoporos Int. doi:10.1007/s00198-015-3236-5
124. Decullier E, Couris CM, Beauchet O, Zamora A, Annweiler C, Dargent Molina P, Schott AM (2010) Falls' and fallers' profiles. J Nutr Health Aging 14(7):602–608
125. Alexander NB, Ulbrich J, Raheja A, Channer D (1997) Rising from the floor in older adults. J Am Geriatr Soc 45(5):564–569
126. Fleming J, Brayne C (2008) Cambridge city over-75s Cohort (CC75C) study collaboration. Inability to get up after falling, subsequent time on floor, and summoning help: prospective cohort study in people over 90. BMJ 337:a2227
127. Bergland A, Laake K (2005) Concurrent and predictive validity of "getting up from lying on the floor". Aging Clin Exp Res 17(3):181–185
128. Ryynänen OP, Kivelä SL, Honkanen R, Laippala P (1992) Falls and lying helpless in the elderly. Z Gerontol 25(4):278–282
129. Tinetti ME, Liu WL, Claus EB (1993) Predictors and prognosis of inability to get up after falls among elderly persons. JAMA 269(1):65–70
130. Schwickert L, Oberle C, Becker C, Lindemann U, Klenk J, Schwenk M, Bourke A, Zijlstra W (2015) Model development to study strategies of younger and older adults getting up from the floor. Aging Clin Exp Res. doi:10.1007/s40520-015-0397-1
131. Ulbrich J, Raheja A, Alexander NB (2000) Body positions used by healthy and frail older adults to rise from the floor. J Am Geriatr Soc 48(12):1626–1632
132. Rolland Y, Dupuy C (2011) Abellan van Kan G, Gillette S, Vellas B. Treatment strategies for sarcopenia and frailty. Med Clin North Am 95(3):427–438
133. 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(4):655–662
134. Straight CR, Lindheimer JB, Brady AO, Dishman RK, Evans EM (2015) Effects of resistance training on lower-extremity muscle power in middle-aged and older adults: a systematic review and meta-analysis of randomized controlled trials. Sports Med. doi:10.1007/s40279-015-0418-4
135. Liu CJ, Latham NK (2009) Progressive resistance strength training for improving physical function in older adults. Cochrane Database Syst Rev. doi:10.1002/14651858.CD002759.pub2
136. Orr R, Raymond J, Fiatarone Singh M (2008) Efficacy of progressive resistance training on balance performance in older adults: a systematic review of randomized controlled trials. Sports Med 38(4):317–343
137. Orr R (2010) Contribution of muscle weakness to postural instability in the elderly. A systematic review. Eur J Phys Rehabil Med 46(2):183–220
138. Holviala J, Kraemer WJ, Sillanpää E, Karppinen H, Avela J, Kauhanen A, Häkkinen A, Häkkinen K (2012) Effects of strength, endurance and combined training on muscle strength, walking speed and dynamic balance in aging men. Eur J Appl Physiol 112(4):1335–1347
139. Holviala J, Häkkinen A, Alen M, Sallinen J, Kraemer W, Häkkinen K (2014) Effects of prolonged and maintenance strength training on force production, walking, and balance in aging women and men. Scand J Med Sci Sports 24(1):224–233
140. Yamashita F, Iwamoto J, Osugi T, Yamazaki M, Takakuwa M (2012) Chair rising exercise is more effective than one-leg standing exercise in improving dynamic body balance: a randomized controlled trial. J Musculoskelet Neuronal Interact 12(2):74–79
141. Lee IH, Park SY (2013) Balance improvement by strength training for the elderly. J Phys Ther Sci 25(12):1591–1593

142. Kim S, Lockhart T (2010) Effects of 8 weeks of balance or weight training for the independently living elderly on the outcomes of induced slips. Int J Rehabil Res 33(1):49–55
143. Pamukoff DN, Haakonssen EC, Zaccaria JA, Madigan ML, Miller ME, Marsh AP (2014) The effects of strength and power training on single-step balance recovery in older adults: a preliminary study. Clin Interv Aging 17(9):697–704
144. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE (2012) Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 9:CD007146
145. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JCT (2008) Effective approaches to exercise in the prevention of falls – a systematic review and meta-analysis. J Am Geriatr Soc 56:2234–2243
146. Davis JC, Marra CA, Robertson MC, Khan KM, Najafzadeh M, Ashe MC, Liu-Ambrose T (2011) Economic evaluation of dose-response resistance training in older women: a cost-effectiveness and cost-utility analysis. Osteoporos Int 22(5):1355–1366
147. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ (1994) Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 330(25):1769–1775
148. Woo J, Hong A, Lau E, Lynn H (2007) A randomised controlled trial of Tai Chi and resistance exercise on bone health, muscle strength and balance in community-living elderly people. Age Ageing 36(3):262–268
149. Latham NK, Anderson CS, Lee A, Bennett DA, Moseley A, Cameron ID, Fitness Collaborative Group (2003) A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). J Am Geriatr Soc 51(3):291–299
150. Province MA, Hadley EC, Hornbrook MC, Lipsitz LA, Miller JP, Mulrow CD, Ory MG, Sattin RW, Tinetti ME, Wolf SL (1995) The effects of exercise on falls in elderly patients. A preplanned meta-analysis of the FICSIT Trials. Frailty and injuries: cooperative studies of intervention techniques. JAMA 273(17):1341–1347
151. Serra-Rexach JA, Bustamante-Ara N, Hierro Villarán M, González Gil P, Sanz Ibáñez MJ, Blanco Sanz N, Ortega Santamaría V, Gutiérrez Sanz N, Marín Prada AB, Gallardo C, Rodríguez Romo G, Ruiz JR, Lucia A (2011) Short-term, light- to moderate-intensity exercise training improves leg muscle strength in the oldest old: a randomized controlled trial. J Am Geriatr Soc 59(4):594–602
152. Donald IP, Pitt K, Armstrong E, Shuttleworth H (2000) Preventing falls on an elderly care rehabilitation ward. Clin Rehabil 14(2):178–185
153. Liu-Ambrose T, Khan KM, Eng JJ, Janssen PA, Lord SR, McKay HA (2004) Resistance and agility training reduce fall risk in women aged 75 to 85 with low bone mass: a 6-month randomized, controlled trial. J Am Geriatr Soc 52(5):657–665
154. Singh NA, Clements KM, Fiatarone MA (1997) A randomized controlled trial of progressive resistance training in depressed elders. J Gerontol A Biol Sci Med Sci 52(1):M27–M35
155. Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC (2010) Resistance training and executive functions: a 12-month randomized controlled trial. Arch Intern Med 170(2):170–178
156. El-Khoury F, Cassou B, Charles MA, Dargent-Molina P (2013) The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. BMJ 29(347):f6234
157. AGS/BGS Clinical Practice Guideline: prevention of falls in older persons: http://www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/prevention_of_falls_summary_of_recommendations. Accessed 11 Sept 2015
158. Miller E, Wightman E, Rumbolt K, McConnell S, Berg K, Devereaux M, Campbell F (2009) Management of fall-related injuries in the elderly: a retrospective chart review of patients presenting to the emergency department of a community-based teaching hospital. Physiother Can 61(1):26–37
159. Donaldson MG, Khan KM, Davis JC, Salter AE, Buchanan J, McKnight D, Janssen PA, Bell M, McKay HA (2005) Emergency department fall-related presentations do not trigger fall risk assessment: a gap in care of high-risk outpatient fallers. Arch Gerontol Geriatr 41(3):311–317
160. Salter AE, Khan KM, Donaldson MG, Davis JC, Buchanan J, Abu-Laban RB, Cook WL, Lord SR, McKay HA (2006) Community-dwelling seniors who present to the emergency department with a fall do not receive Guideline care and their fall risk profile worsens significantly: a 6-month prospective study. Osteoporos Int 17(5):672–683
161. Crombie IK, Irvine L, Williams B, McGinnis AR, Slane PW, Alder EM, McMurdo ME (2004) Why older people do not participate in leisure time physical activity: a survey of activity levels, beliefs and deterrents. Age Ageing 33(3):287–292
162. Elskamp AB, Hartholt KA, Patka P, van Beeck EF, van der Cammen TJ (2012) Why older people refuse to participate in falls prevention trials: a qualitative study. Exp Gerontol 47(4):342–345
163. Høst D, Hendriksen C, Borup I (2011) Older people's perception of and coping with falling, and their motivation for fall-prevention programmes. Scand J Public Health 39(7):742–748
164. Yardley L, Bishop FL, Beyer N, Hauer K, Kempen GI, Piot-Ziegler C, Todd CJ, Cuttelod T, Horne M, Lanta K, Holt AR (2006) Older people's views of falls-prevention interventions in six European countries. Gerontologist 46(5):650–660
165. Lam FM, Lau RW, Chung RC, Pang MY (2012) The effect of whole body vibration on balance, mobility and falls in older adults: A systematic review and meta-analysis. Maturitas 72:206–213
166. Leung KS, Li CY, Tse YK, Choy TK, Leung PC, Hung VW, Chan SY, Leung AH, Cheung WH (2014) Effects of 18-month low-magnitude high-frequency vibration on fall rate and fracture risks in 710 community elderly—a cluster-randomized controlled trial. Osteoporos Int 25(6):1785–1795
167. Benavent-Caballer V, Rosado-Calatayud P, Segura-Ortí E, Amer-Cuenca JJ, Lisón JF (2014) Effects of three different low-intensity exercise interventions on physical performance, muscle CSA and activities of daily living: a randomized controlled trial. Exp Gerontol 58:159–165
168. Mansfield A, Wong JS, Bryce J, Knorr S, Patterson KK (2015) Does perturbation-based balance training prevent falls? Systematic review and meta-analysis of preliminary randomized controlled trials. Phys Ther 95(5):700–709
169. Chien MH, Guo HR (2014) Nutritional status and falls in community-dwelling older people: a longitudinal study of a population-based random sample. PLoS One 9(3):e91044
170. Neyens J, Halfens R, Spreeuwenberg M, Meijers J, Luiking Y, Verlaan G, Schols J (2013) Malnutrition is associated with an increased risk of falls and impaired activity in elderly patients in Dutch residential long-term care (LTC): a cross-sectional study. Arch Gerontol Geriatr 56(1):265–269
171. Travison TG, Basaria S, Storer TW, Jette AM, Miciek R, Farwell WR, Choong K, Lakshman K, Mazer NA, Coviello AD, Knapp PE, Ulloor J, Zhang A, Brooks B, Nguyen AH, Eder R, LeBrasseur N, Elmi A, Appleman E, Hede-Brierley L, Bhasin G, Bhatia A, Lazzari A, Davis S, Ni P, Collins L, Bhasin S (2011) Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone

administration in older men with mobility limitation. J Gerontol A Biol Sci Med Sci 66(10):1090–1099
172. Dobs AS, Boccia RV, Croot CC, Gabrail NY, Dalton JT, Hancock ML, Johnston MA, Steiner MS (2013) Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. Lancet Oncol 14(4):335–345
173. Scutti S (2013) Enobosarm, GTx Lung Cancer Drug, Fails In Late-Stage Trials To Test Muscle-Wasting Prevention And Treatment. http://www.medicaldaily.com/enobosarm-gtx-lung-cancer-drug-fails-late-stage-trials-test-muscle-wasting-prevention-and-treatment. Accessed 11 Sept 2015
174. Dalton JT, Taylor RP, Mohler ML, Steiner MS (2013) Selective androgen receptor modulators for the prevention and treatment of muscle wasting associated with cancer. Curr Opin Support Palliat Care 7(4):345–351
175. Becker C, Lord SR, Studenski SA, Warden SJ, Fielding RA, Recknor CP, Hochberg MC, Ferrari SL, Blain H, Blain H, Binder EF, Rolland Y, Poiraudeau S, Benson CT, Myers SL, Hu L, Ahmad QI, Pacuch KR, Gomez EV, Benichou O, STEADY Group (2015) Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial. Lancet Diabetes Endocrinol 3(12):948–957
176. Amato AA, Sivakumar K, Goyal N, David WS, Salajegheh M, Praestgaard J, Lach-Trifilieff E, Trendelenburg AU, Laurent D, Glass DJ, Roubenoff R, Tseng BS, Greenberg SA (2014) Treatment of sporadic inclusion body myositis with bimagrumab. Neurology 83(24):2239–2246
177. Gibson MJ, Andres RO, Isaacs B, Radebaugh T, Worm-Petersen J (1987) The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. Dan Med Bull 34(Suppl 4):1–24
178. Lamb SE, Jørstad-Stein EC, Hauer K, Becker C, Prevention of Falls Network Europe and Outcomes Consensus Group (2005) Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. J Am Geriatr Soc 53(9):1618–1622
179. Campbell AJ, Robertson MC (2007) Rethinking individual and community fall prevention strategies: a meta-regression comparing single and multifactorial interventions. Age Ageing 36(6):656–662
180. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen, Wiklund O, ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees et al (2011) ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 32(14):1769–1818
181. Bruckert E, Ferrières J (2014) Evidence supporting primary prevention of cardiovascular diseases with statins: gaps between updated clinical results and actual practice. Arch Cardiovasc Dis 107(3):188–200
182. Laussen JC, Chalé A, Hau C, Fielding RA, White DK (2015) Does physical activity change after progressive resistance exercise in functionally limited older adults? J Am Geriatr Soc 63(2):392–393
183. Granacher U, Zahner L, Gollhofer A (2008) Strength, power, and postural control in seniors: considerations for functional adaptations and for fall prevention. Eur J Sport Sci 8(6):325–340
184. Gerdhem P, Ringsberg KA, Akesson K, Obrant KJ (2003) Influence of muscle strength, physical activity and weight on bone mass in a population-based sample of 1004 elderly women. Osteoporos Int 14(9):768–772
185. Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell TJ, Tricker R, Shirazi A, Casaburi R (1996) The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 335(1):1–7
186. Hildreth KL, Barry DW, Moreau KL, Vande Griend J, Meacham RB, Nakamura T, Wolfe P, Kohrt WM, Ruscin JM, Kittelson J, Cress ME, Ballard R, Schwartz RS (2013) Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. J Clin Endocrinol Metab 98(5):1891–1900