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## Exercise as an Intervention for Frailty

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### Keywords

exercise; frailty; elderly; older adults

### Introduction

By 2015, nearly 15% of the U.S. population will be over the age of 65. In 2030, there will be over 70 million older Americans<sup>1</sup>. This increase in the elderly population has prompted interest in recent years toward the study of “frail” older adults. Clinicians use the term “frail” to describe a person over 65 years old who is vulnerable to any kind of change in health status, such as infection or physical injury<sup>2</sup>. These individuals are at high risk of complications during a medical illness and have prolonged recovery times<sup>3</sup>. An international consensus report in 2006 characterized frail elders as having impairments in mobility, balance, strength, motor processing, cognition, nutrition, endurance (fatigue) and physical activity<sup>4</sup>.

In 1992, Buchner first proposed a formal definition of frailty as a syndrome of weakness, impaired mobility, balance, and minimal reserve<sup>5</sup>. Using epidemiological data from the Cardiovascular Health Study (CHS), Fried further characterized frailty as individuals who had unintentional weight loss (ten or more pounds in the past year), fatigue or exercise intolerance, weakness, slowed motor performance, and low physical activity. A person was considered frail if they demonstrated at least three of these attributes (see Figure 1), and pre-frail if they had one or two of these characteristics. Fried found those who were frail had an increased risk of falls, ADL disability, hospitalization, and death over a three year period<sup>2</sup>. In the Women’s Health and Aging I (WHAS-I) study, the risk of ADL dependence increased with the number of frailty criteria fulfilled<sup>6</sup>. Mortality in the frail cohort of the Cardiovascular Health Study was approximately three times higher when compared to the non-frail cohort (43% versus 12%) at seven years. Interestingly, 25% of frail subjects in the Cardiovascular Health Study had only one chronic disease, defined as osteoarthritis, diabetes, hypertension, angina, congestive heart failure, cancer or pulmonary disease<sup>2</sup>,

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suggesting that frailty was not always associated with multiple co-morbidities. The underlying mechanisms causing the phenotype of frailty remain to be fully elucidated. Buchner and Wagner initially proposed that declines in neurological processes, musculoskeletal functioning, and energy metabolism were the cause of frailty<sup>5</sup>. Lipsitz later suggested that frailty might be caused by the loss of the ability of the cardiovascular and nervous systems to respond appropriately to stressors due to age-related changes<sup>7</sup>. Using these concepts, frailty is now thought to be due altered function in multiple physiological systems (including inflammatory, skeletal muscle, endocrine, clotting, and hematological) and dysregulation of mechanisms between these systems to maintain homeostasis<sup>8</sup>.

With increasing age, there is a well-described decline in voluntary physical activity which is associated with decreases in several measures of exercise tolerance including maximal aerobic capacity, muscle strength, and fatigueability<sup>9</sup>, leading to an increase risk of frailty. In recent years, increased physical activity or regular exercise training has been proposed as preventive strategies for frailty and its adverse outcomes, as it can target four of the frailty criteria: weakness, low physical activity, slowed motor performance, and exercise intolerance. Epidemiological studies suggest that regular physical activity is associated with a decreased risk of ADL disability in older adults, which is an adverse outcome of frailty. In a large scale cohort study done in Taiwan, Wu et al found older adults who were physically active, defined as participation in dancing, hiking, jogging or walking at least twice a week, were less likely to have ADL disabilities at the end of a three year period when compared to their sedentary counterparts<sup>10</sup>. These findings were confirmed by the Longitudinal Study of Aging, which found elders who were physically active, defined a walking at least a mile a week, were less likely to develop impairments in their ADL/IADLs over a six year period, after adjusting for age, gender, co-morbidities, and baseline disability<sup>11</sup>.

The major goal of this chapter is to review the literature investigating the utility of aerobic and resistance exercise training as an intervention for frailty in older adults. In addition, areas of future research will be addressed, including concerns related to the dissemination of exercise interventions on a widespread scale. Finally, guidelines for an “exercise prescription” for frail older adults will be briefly outlined.

## Aerobic/endurance exercise training

There are two mechanisms by which aerobic exercise is thought to alter the frailty phenotype: improvement in the maximal oxygen uptake ( $VO_2$  peak) and increased muscle mass.  $VO_2$  peak is defined as the maximum rate of oxygen consumption measured during vigorous exercise and is closely related to sub-maximal endurance exercise capacity and exercise tolerance.

In an intervention study of 64 frail men and women, a nine month program of strength training and walking aimed at reaching 78% of peak heart rate was found to increase endurance by improving  $VO_2$  peak by 14%<sup>12</sup>. A small study of healthy elderly sedentary women also found a 12 week regimen of cycle ergometer training improved maximal aerobic capacity by 30% from baseline. This study demonstrated that the endurance training increased quadriceps muscle mass by 12%<sup>13</sup>. Although previous studies have shown that aerobic exercise did not alter muscle size in older adults<sup>14–16</sup>, a recent cross-sectional study by Sugawara<sup>17</sup> demonstrated that those who undergo aerobic training have a higher percentage of muscle mass in their extremities when compared to their sedentary counterparts.

## Resistance exercise training

There is well-documented evidence that muscle strength decreases with advancing age. Muscle strength decreases approximately 12% to 15% per decade after the age of 50 years<sup>18</sup> in both males and females<sup>19</sup>. Additionally, muscle mass also decreases with increased age. In a cross-sectional study of healthy men of equal mass, muscle mass comprised 24% of total mass in those 20 to 29 years old, but decreased to 13% in subjects aged 70 to 79 years<sup>20</sup>. Several studies have found that the decline in strength in the older adult is due to this age-related loss of muscle mass<sup>21–23</sup>. While resistance exercise training has been shown to increase muscle mass and therefore muscle strength, this response is attenuated in older adults with mobility limitations or other co-morbidities. In healthy older men and women, four months of resistance training resulted in a 16 to 23% increase in muscle mass, compared to a 2.5–9% increase in frail or institutionalized older adults<sup>24–26</sup>.

Despite these age-related effects on muscle, resistance exercise training still has been found to increase strength in older adults. Multiple studies have demonstrated that these changes can occur even into the ninth decade of life<sup>24, 27–31</sup>. In a systemic review of 41 articles by Latham, resistance exercise training in older adults was associated with gains in strength<sup>32</sup>, and a Cochrane review of 74 studies found similar results<sup>33</sup>. Both reviews used studies that examined both healthy older adults and frail adults. Of note, Fiatarone showed nursing home residents were able to increase their strength on average 97% after 10 weeks of resistance exercise training<sup>25</sup>. As nursing home residents represent the frailest segment of older adults, this demonstrates the intervention is beneficial for even those most severely affected.

Motor performance in older adults has also been shown to improve after resistance training. In her systemic review, Latham found resistance exercise training in healthy and frail elders improved gait speed in 14 studies and increased distances in the six minute walk test in six trials<sup>32</sup>. In their respective studies of frail elders living in the nursing home and in the community, Fiatarone and Chandler each showed that 10 weeks of resistance training resulted in improved gait speed<sup>25, 34</sup>. There may be a dose response relationship between resistance exercise and motor performance, as Galvao and Taaffe found subjects who did more repetitions of resistance exercise had almost twice the improvement in their 400 meter walk time compared to those who did fewer repetitions<sup>35</sup>.

## Combined aerobic and resistance exercise

Given the beneficial results seen with aerobic or resistance exercise alone and that both types of exercise target specific distinct features of frailty, there has been recent interest in whether an intervention with both components is beneficial for frail older adults. In a randomized controlled trial of elderly subjects who had undergone surgical repair of a femur fracture, a six month intervention of aerobic activity and progressive resistance exercise was associated with a mean improvement of 19 meters per minute in walking speed<sup>36</sup>. Similar changes in motor function were demonstrated in the Lifestyles Interventions and Independence for Elders (LIFE) study, which found that a 12 month program of walking, resistance exercise, and flexibility training improved scores on the Short Physical Performance Battery (SPPB) and prevented a decline in 400 meter walk speed in older adults at high risk for disability one year after follow up<sup>37</sup>.

## Effect of exercise interventions on the adverse outcomes of frailty

Several studies have examined the effect of exercise on falls, a common adverse outcome of frailty. After a single fall, the risk of skilled nursing facility placement in older adults increases three-fold, after adjustment for cognitive, psychological, social, functional and medical factors<sup>38</sup>. In a study examining women undergoing resistance training for 25

weeks, risk of falls was reduced by 57% from baseline<sup>39</sup>. A meta-analysis of six studies by Baker showed a combined regimen of aerobic, resistance, balance and flexibility exercises was found to decrease fall risk<sup>40</sup>. A Cochrane review of 111 trials found that a combination of aerobic and resistance exercise reduced the risk of falls by 17% in community dwelling elders<sup>41</sup>.

In addition to falls, ADL disability is of major concern in frail individuals as it is associated with higher rates of mortality<sup>42</sup>. In the systemic review of 41 studies conducted by Latham<sup>32</sup>, resistance exercise training did not decrease the risk of ADL disability in an elderly population. In contrast, a Cochrane review of 121 trials found an association between resistance training and reduced ADL disability<sup>33</sup>. Neither review stratified their results by frailty severity. In a randomized controlled trial of a six month home-based program that combined resistance exercise training with balance training and home safety and assistive device evaluations, rates of ADL disability decreased only in those with moderate frailty, but not in those with not in those with severe frailty. Moderate frailty was defined as either the inability to perform a rapid gait test (requiring more than 10 seconds to walk a 3 meter course) or stand up from a chair with arms folded, and severe frailty was defined as having both characteristics<sup>43, 44</sup>. In contrast, Binder did not find an improvement in the Older American Resources and Services (OARS) ADL score in a group of mild to moderately frail subjects<sup>45</sup> after a regimen of resistance, balance, and flexibility training. Currently, final results of the FRASI (FRailty, Screening and Intervention) are pending, and will look at the effect of an eight week exercise regimen on the on the time of onset of ADL disability in community dwelling frail elders<sup>46</sup>. Table 1 lists key randomized controlled trials that studied frail older adults (Table 1).

## Effect on the phenotype of frailty

Although there have been multiple trials studying the effects of exercise on the various characteristics of frailty and the adverse outcomes of frailty, there have been relatively few studies to see whether exercise can alter or even reverse frailty status in older adults. In a study conducted with subjects who were frail or at high risk for frailty, a telephone intervention encouraging exercise decreased the proportion of frail elders by 18% at 6 months follow-up<sup>47</sup>. Currently, the Frailty Intervention Trial (FIT) study is examining whether a 12 month intervention of aerobic and resistance training can change frailty status in a cohort of already frail older adults<sup>48</sup>.

## Adverse outcomes of exercise

Reports of adverse outcomes with both aerobic and resistance training while not uncommon, are rarely life threatening. In a study that examined resistance training in elderly women, most of the adverse outcomes were musculoskeletal complaints<sup>39</sup>. Latham found that the risk ratio for adverse events increased to 3.6 in those who underwent of ten weeks of resistance training<sup>49</sup>. However, no reports of death or cardiovascular events were found in a systemic review of 62 trials of resistance exercise<sup>32</sup>. In a randomized controlled trial studying the effect of a 12 month intervention of walking, resistance exercise, and flexibility, similar rates of serious and non-serious adverse events were found for both the intervention and control subjects<sup>37</sup>.

## Future Directions

Clearly, exercise and physical activity are promising interventions for frailty, and several studies are currently underway to examine their impact. However, there are several related areas that need further investigation this intervention can be disseminated to frail older adults on a widespread basis. First, adherence to an exercise regimen is key to its beneficial

effects, and strategies to overcome this barrier need to be developed before exercise as treatment modality is implemented on a wide scale. Schneider found that subjects were interested in exercise for its medical and psychological benefits, but had concerns about the time required and about their abilities to perform adequate exercise<sup>50</sup>. In addition, cognition is a factor that should be considered. A significant proportion of older adults are cognitively impaired, which may impact their ability to properly adhere to a regular exercise regimen. However, if caregivers are involved, this may not be such a barrier. In a randomized clinical trial, subjects with Alzheimer's dementia participated in a home-based exercise program of aerobic and resistance exercise under the supervision of their caregivers. At three months, the dementia subjects were more active and had better motor functioning compared to the controls<sup>51</sup>. Almost all the trials reviewed in this chapter were clinic or facility based. Home-based programs are more accessible, and would eliminate the barrier of transportation for many elders. In a study that examined a six month home-based program that combined resistance and balance training with home safety and assistive device evaluations, there was no improvement in motor performance. However, a later Cochrane review did find that home-based exercise programs reduced the risk of falls in older adults by 23%<sup>41</sup>. Finally, whether these exercise interventions would require supervision by a rehabilitation professional or could be conducted in the community, is still unclear. If supervision is necessary, this adds to the cost of the intervention. Future and ongoing trials should include an analysis of the costs and benefits of a physical activity intervention.

## Conclusion: An exercise “prescription”

While more investigation is still needed, the majority of studies suggest that clinicians should recommend regular physical activity or exercise training to frail older adults. The current guidelines from the U.S. Department of Health and Human Services state that all adults over 65 years should participate in 150 minutes (2 hours and 30 minutes) of moderate aerobic exercise per week<sup>52</sup>. Although most trials studied resistance exercise training, we would encourage frail older adults to start with an aerobic activity such as walking, as it is more accessible. If possible, resistance exercise training should be added. Depending on the degree of frailty, supervision may or may not be required. For individuals with severe frailty, evaluation by a rehabilitation profession is recommended.

The majority of evidence shows that regular physical activity or exercise is beneficial for older adults who are frail or at high risk of frailty. Studies have shown the number adverse events are minimal, and the gains of regular exercise clearly outweigh the risks. Although there are still several areas related to the intervention that require further investigation, for older adults regular physical activity or exercise is highly recommended as a means to modify frailty and its adverse outcomes.

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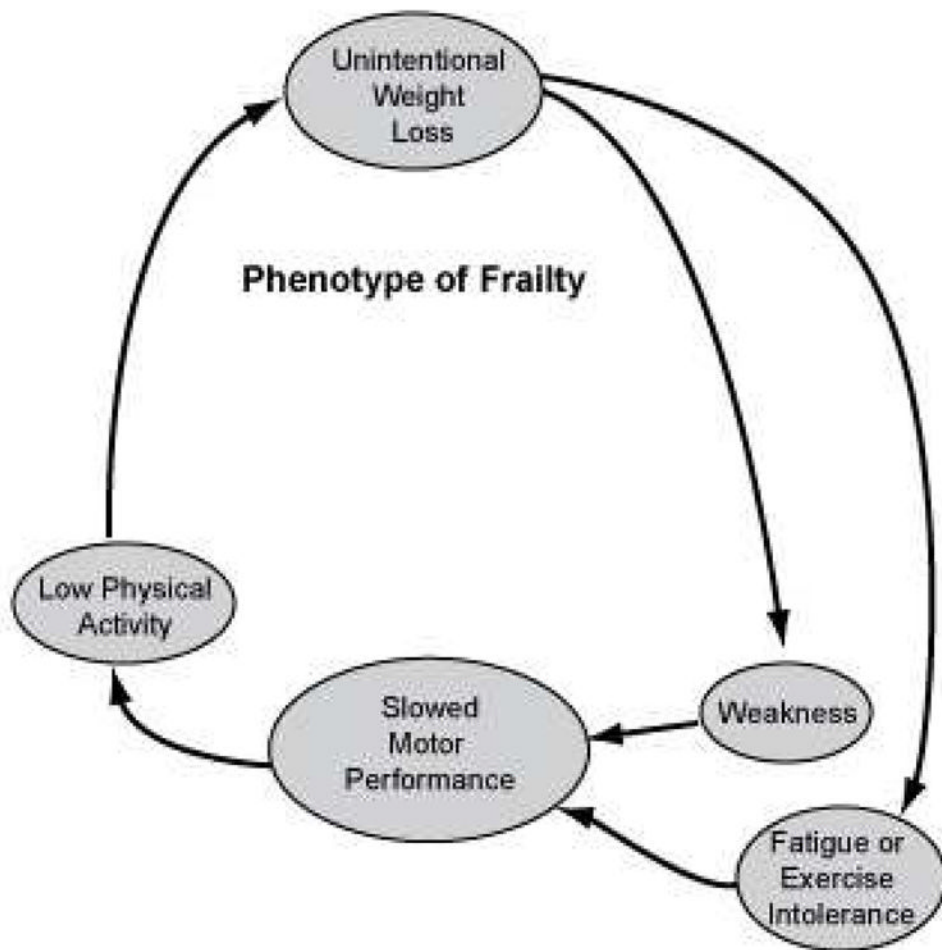
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**Figure 1. Components of frailty**

Adapted from Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci.* Oct 2009;64(10): 1050.

Table 1

## Randomized controlled trials in frail older adults

Study	Population	Intervention	Outcome
<b>Fiatarone et al 1994</b> <sup>25</sup>	Nursing home residents 70 years or older and able to walk 6 meters	3 sessions per week of resistance training of lower extremities for 10 weeks versus regular recreational activities	Mean improvement in muscle strength of lower extremities was 97% for intervention group compared to 12% for control group
<b>Chandler et al 1998</b> <sup>34</sup>	Community dwelling older adults 65 years and older and unable to climb stairs without a handrail	3 sessions per week of progressive resistance training of lower extremities with stair stepping and chair rises for 10 weeks versus normal activities	Mean improvement in muscle strength of lower extremities was 10 to 13% for intervention group compared to 1% improvement to 3% decline in control group
<b>Binder et al 2002</b> <sup>45</sup>	Community dwelling older adults 78 years and older who had 2 of the following criteria: modified PPT score 18 to 32, VO <sub>2</sub> peak 10 to 18 mL/kg/min, or difficulty with either 1 ADL or 2 IADLs	3 sessions a week of resistance training of upper and lower extremities, aerobic training with walking, cycling or rowing, and flexibility/balance training for 9 months versus flexibility exercises	Mean improvement in lower extremity strength was 19% to 23% for intervention group compared to 5% improvement to 5% decline in control group Mean VO <sub>2</sub> peak improved 13% for intervention group compared to 2.6% decline in control group
<b>Gill 2002</b> <sup>44</sup>	Community dwelling older adults 75 years and older who required more than 10 seconds to walk 3 meters and/or unable to stand up from a chair with arms folded	Average of 16 sessions in the home of resistance training of upper and lower extremities, flexibility and balance exercises, and home safety and assistive device evaluations for 6 months versus education program	66% improvement in disability scores for those with moderate frailty but no significant improvement for those with severe frailty in intervention group, using control group as baseline