Lifestyle Intervention Strategies to Treat Frailty in Older Adults with Obesity

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Why Lifestyle Intervention?
- Frailty could be due to unhealthy lifestyles.
- Frailty could be due to treatable lifestyle factors.
  - undernutrition (e.g. protein deficiency)
  - overnutrition (e.g. sarcopenic obesity)
  - ↓ physical activity (e.g. exercise deficiency)
- Lifestyle factors may be more controllable.
- Lifestyle intervention is any intervention that includes
  - diet
  - exercise
  - other components
    - counseling
    - stress management
    - behavioral therapy
- Comprehensive lifestyle interventions

Diet during Aging
- Dietary factors contributing to frailty
  - Inadequate protein intake
  - Reduced anabolic response to nutrients
  - Older adults should probably consume 1.0-1.2/kg/day.
  - The patterns of intake may be important.
  - There may be a threshold for maximal stimulus of MPS.

Exercise during Aging
- % undertaking PA
- Peak VO₂
  - Aerobic exercise
  - Strength
  - Resistance exercise

Systematic Reviews: Interventions to Prevent or Reduce Frailty

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Journal</th>
<th>Inclusion Criteria</th>
<th>No. of Distinct RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021</td>
<td>Racey et al</td>
<td>CMAJ Open</td>
<td>Age ≥ 65 y; prefrail or frail</td>
<td>15 RCTs, 1825 patients</td>
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<tr>
<td>2019</td>
<td>Kidd et al</td>
<td>BMC Geriatrics</td>
<td>Age ≥ 65 y; prefrail or frail</td>
<td>10 RCTs</td>
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<tr>
<td>2019</td>
<td>Liu et al</td>
<td>Curr Geri Rep</td>
<td>M/Mdn age ≥ 65 y; frailty measures</td>
<td>10 RTCs</td>
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<td>2018</td>
<td>Watson et al</td>
<td>Clin Geriatr Med</td>
<td>Age ≥ 65 y; prefrail or frail</td>
<td>20 RCTs</td>
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<td>2018</td>
<td>Apostolo et al</td>
<td>JBI Database</td>
<td>Age ≥ 65 y; prefrail or frail</td>
<td>21 RCTs, 5275 patients</td>
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<tr>
<td>2017</td>
<td>Puts et al</td>
<td>Age and Ageing</td>
<td>Age ≥ 65 y; frailty measures</td>
<td>14 RCTs, 2 cohort studies</td>
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<tr>
<td>2015</td>
<td>Labra et al</td>
<td>BMC Geriatr</td>
<td>&quot;Frail elderly&quot;, exercise interventions</td>
<td>9 RCTs, 1067 patients</td>
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<tr>
<td>2011</td>
<td>Theou et al</td>
<td>J Aging Res</td>
<td>&quot;Frail&quot;, exercise interventions</td>
<td>47 RCTs</td>
</tr>
</tbody>
</table>

- Frailty interventions included exercise, nutrition, and multicomponent strategies, though findings to date have been mixed.
- Exercise programs were shown to be generally effective for reducing frailty but only when conducted in groups.
- Favorable effects were also observed for exercise with supplementation, supplementation alone, cognitive training, and combined treatment.
- Multicomponent exercise of ≥ 5 months, 3x/week, 30-45 minutes, generally had superior outcomes than other exercise programs.
**Frailty in Older Adults with Obesity**

Muscle quality = strength/muscle mass

Villareal et al., Obes Res 12, 913-920, 2004

Blaum et al., J Am Geriatr Soc 53, 927-934, 2005

**Fat Frail**

Visceral obesity

Sarcopenic obesity

**Obesity Is Not Protective against Fracture in Postmenopausal Women**

- Global Longitudinal study in Osteoporosis in Women (GLOW)
- 60,393 women aged ≥55 yrs.
- 44,504 (74%) were obese
**Diet Therapy**
- **Balanced Diet**
  - Provide energy deficit of ~750 kcal/day
  - Goal of 10% weight loss
- **Weekly Group Behavioral Therapy**
  - Goal setting
  - Self-monitoring
  - Stimulus control
  - Problem solving skills
  - Relapse prevention training

**Exercise Therapy**
- **Group Exercise-Training Sessions**
  - 3 nonconsecutive days a week
  - Supervised by a physical therapist
  - 15-min flexibility
  - 30-min endurance (~80% of VO2peak)
  - 30-min resistance (~80% of 1-RM)
  - 15-min balance

**Diet and Exercise Therapy Ameliorates Frailty**

**Diet and Exercise Therapy Improves Pancreatic Endocrine Secretion**

**Diet and Exercise Therapy decreases BMD and increases Bone Turnover**

**Obesity in Older Adults: Technical Review and Position Statement of the American Society for Nutrition and NAASO, The Obesity Society**

- The current data show that
  - Weight-loss therapy improves physical function, quality of life, and the medical complications associated with obesity in older persons.
- Weight-loss therapy that minimizes muscle and bone losses is recommended for older persons who
  - are obese
  - have functional impairments or medical complications that can benefit from weight loss
In older adults

• Improving physical function and quality of life may be the most important goals of therapy

Guidelines – interim recommendations

• May change as further research and information become available

The Combination of Weight Loss and Exercise Provides Greater Improvement in Physical Function than either Intervention alone

Changes in Specific Physical Functions during the 1-yr Intervention

Weight Loss Therapy Improves Body Composition
Exercise added to Weight Loss Therapy Preserves Muscle Mass

Before (Wt = 91 kg)
- Fat = 42 kg
- Lean = 49 kg
- Relative Lean = 54%
- PPT = 25 (Frail)

After (Wt = 82 kg)
- Fat = 34 kg
- Lean = 50 kg
- Relative Lean = 60%
- PPT = 30 (NonFrail)

Exercise but not Diet Suppresses Muscle Inflammatory Gene Expression in Obese Elderly

Before (Wt = 91 kg)

- 12 kg Fat
- +1 kg Lean
- -18%
- +4%

Interleukin-6
Tumor necrosis factor-α
Mechano growth factor

Exercise Training in Obese Older Adults Prevents Increase in Bone Turnover and Attenuates Decrease in Hip BMD induced by Weight loss Despite Decline in Bone-Active Hormones

Changes in thigh muscle volume predict bone mineral density response to lifestyle therapy in frail, obese older adults

Weight Loss in Obese Older Adults Increases Serum Sclerosin but is Prevented by Exercise Training
**Independent and Additive Effects of Weight Loss and Exercise on Insulin Sensitivity in Older Adults with Obesity**

Effect of Diet on insulin sensitivity may be contingent upon preceding weight loss.

**Diet and Exercise Therapies Improve Cognition in Older Adults with Obesity**

The combination of diet and exercise provided cognitive benefits equivalent to exercise alone.

**Diet and Exercise Therapies Improve Impact of Weight on Quality of Life (IWQOL)**

Diet + exercise = Exercise

- The combination of diet and exercise provided cognitive benefits equivalent to exercise alone.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Diet</th>
<th>Exercise</th>
<th>Additive</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>↓↓</td>
<td>↓</td>
<td>yes</td>
<td>In purpose for weight loss therapy</td>
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<tr>
<td>Fat mass</td>
<td>↓↓</td>
<td>↓</td>
<td>yes</td>
<td>Exercise does not prevent (but attenuation) weight loss-induced muscle and bone mass.</td>
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<tr>
<td>Fat-free mass</td>
<td>↓</td>
<td>↑</td>
<td>-</td>
<td>Exercise does not prevent (but attenuation) weight loss-induced muscle and bone mass.</td>
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<tr>
<td>Quality of life</td>
<td>↑</td>
<td>↓</td>
<td>yes</td>
<td>Combined + exercise</td>
</tr>
<tr>
<td>Cognition</td>
<td>↑</td>
<td>↑</td>
<td>yes</td>
<td>Combined + exercise</td>
</tr>
<tr>
<td>Mus/skel injuries</td>
<td>-</td>
<td>↑</td>
<td>-</td>
<td>Combined + exercise</td>
</tr>
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</table>

**Which distinct type of physical exercise is best to combine with diet-induced weight loss?**

- 160 older (age ≥ 65 yrs) adults with obesity (BMI ≥ 30 kg/m²)
- Randomized to
  - Control
  - Diet + Aerobic
  - Diet + Resistance
  - Diet + Aerobic/Resistance

**Weight Loss plus Combined Aerobic and Resistance Exercise was the most Effective in Improving Functional Status of Obese Older Adults**

- Physical Performance Test (PPT)

<table>
<thead>
<tr>
<th>Week</th>
<th>Diet + Aerobic/Resistance</th>
<th>Diet + Aerobic</th>
<th>Diet + Resistance</th>
<th>Control</th>
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<tr>
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<td>12</td>
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<td>24</td>
<td>40</td>
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<td>44</td>
<td>46</td>
</tr>
</tbody>
</table>
Resistance and Combined Aerobic and Resistance Training Attenuated the Loss of Lean Mass and Hip BMD during Aerobic Training in Obese Older Adults

Aerobic Plus Resistance Exercise is Most Effective in Improving Ectopic Fat and Insulin Sensitivity in Older Adults with Obesity during Weight Loss.

Waters et al., J Nutr Health Aging 17; 3-7, 2013

Aerobic Plus Resistance Exercise in Older Adults with Obesity Improves Muscle Protein Synthesis Despite Weight Loss

Colleluori et al., Cell Metab 30: 261-273, 2019

Aerobic Plus Resistance Exercise in Older Adults with Obesity Improves Muscle Quality Despite Weight Loss

Colleluori et al., Cell Metab 30: 261-273, 2019

Effect of Aerobic or Resistance Exercise, or Both, on Bone Mineral Density and Bone Metabolism in Obese Older Adults While Dieting

Armamenti-Villareal al, J Bone Miner Res 35:430-439, 2020

Long Term Maintenance of Weight Loss After Lifestyle Intervention in Frail, Obese Older Adults

Waters et al., J Nutr Health Aging 17; 3-7, 2013

Does Lifestyle Intervention Improve Bone Quality despite Decline in BMD?

Clinical Trials.gov NCT03329963

FEA of QCT

HF-pQCT

MRI-pQCT
Testosterone Replacement Therapy Added to Intensive Lifestyle Intervention in Older Men With Obesity and Hypogonadism (LITROS - NCT02367105)

- Inclusion criteria
  - Older veterans (age ≥ 65 yrs.)
  - Obese (BMI ≥ 30 kg/m²)
  - Persistently low Am testosterone (<10 nmol/L)
  - Physical frailty (PPT score < 31, low VO₂)
- Randomized to
  - Lifestyle therapy + Placebo (n = 41)
  - Lifestyle therapy + Testosterone (n = 42)

Testosterone Replacement attenuated the Weight Loss–Induced Reduction of Muscle Mass and BMD and Further Improved Aerobic Capacity

Testosterone Augmentation of the Positive Effects of Lifestyle Intervention on Cognitive Function

Effect of Testosterone Replacement added to Intensive Lifestyle Intervention on the Hormone Profile of Older Adults with Obesity and Hypogonadism

Lifestyle Intervention in Seniors with Diabetes (LISD) (NCT022348801)

- Inclusion criteria
  - Older adults (age ≥ 65 yrs.)
  - Overweight/obese (BMI ≥ 27 kg/m²)
  - Type 2 diabetes (medical records, current treatment, health provider, ↑FBG, A1c ≥ 6.5%)
- Randomized to
  - Lifestyle therapy (diet and exercise at facility, → community-fitness centers and homes) (n = 50)
  - Healthy lifestyle (n = 50)

Effect of the Lifestyle Intervention on Body Weight and OGTT Variables
Effect of the Lifestyle Intervention on Glucometabolic Regulation in Older Adults with Diabetes

Effect of the Lifestyle Intervention on Insulin Dose Requirements in Older Adults with Diabetes

Effect of the Lifestyle Intervention on Physical Function and Quality of Life in Older Adults with Diabetes

Effect of Diet, Exercise, or Both on Biological Age and Healthy Aging in Older Adults with Obesity

Summary

- In older adults with obesity and frailty, diet-induced weight loss but not exercise-induced weight loss ↓ muscle and bone mass.
- Exercise added to diet attenuates the weight loss-induced ↓ muscle and bone mass and further ↑ physical function by:
  - ↑ muscle protein synthesis and ↑ muscle quality
  - ↓ bone turnover through skeletal loading and ↓ sclerostin
- Additional strategies to preserve muscle and bone mass
  - ↑ efficiency of protein intake, ↑ weight-bearing exercise, and perhaps anabolic hormone therapy
- Testosterone added to lifestyle intervention may preserve lean body mass in older, obese hypogonadal men.
- A lifestyle intervention strategy may improve glycemic control and functional status in older adults with diabetes.
- Multifactorial interventions are likely to be the most successful in ameliorating frailty.