Physical activity to prevent disability and frailty in older adults - The LIFE Study

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www.aging.ufl.edu
Marco Pahor, MD - Funding disclosure

NIH

- Claude Pepper Older Americans Independence Center P30AG028740
- The LIFE Study U01AG022376
- The Testosterone Trial (TTrial) U01AG030644
- Institute on Aging Clinical Translational Research Building C06RR029852
- Clinical Translational Science Award U54RR025208

Regeneron and Sanofi research grant
Sarcopenia in the context of the International Classification of Function (ICF) model

**Biology**
nervous transmission, hormones, proteolysis, autophagy, apoptosis, satellite cells, inflammation, oxidative stress, energy production, blood flow

**Aging**

**Body (physiological) functions & Body structure**

**Sarcopenia**
Muscle atrophy & intramuscular adipose

**Dynapenia**
Loss of muscle strength

**Activity limitations**
Difficulties in executing tasks

**Environmental**

**Personal factors**

**↑ Healthcare cost**

**↑ Caretaker Stress**

**↓ Independence**

**Participation**
In life situations

**Aging**

**Disease**
metabolic, pulmonary, vascular, immune, organ-specific

**↑ Independence**

**↓ Healthcare cost**

**↑ Caretaker Stress**

**Buford et al. Ageing Research Reviews 2010**
Fat accumulation within skeletal muscle is associated with muscle weakness and the loss of function in older adults. The effects of physical activity on fat within muscle in older adults are not clear.
Frailty in Older Adults: Evidence for a Phenotype

Linda P. Fried

Journal of Gerontology: MEDICAL SCIENCES

Chronic Undernutrition
[Inadequate intake of protein and energy; micronutrient deficiencies]

Neuroendocrine Dysregulation
Anorexia of aging

↓ Total Energy Expenditure
↓ Activity
↓ Walking Speed
Disability
Dependency

↓ Resting Metabolic Rate

↓ Strength & Power

↓ VO₂max

Aging: Senescent musculoskeletal changes
Negative Energy Balance
Negative Nitrogen Balance

Weight Loss

Loss of muscle mass
Sarcopenia

Disease
### A. Characteristics of Frailty

- **Shrinking:** Weight loss (unintentional)
- **Sarcopenia:** Loss of muscle mass
- **Weakness**
- **Poor endurance; Exhaustion**
- **Slowness**
- **Low activity**

### B. Cardiovascular Health Study Measure*

- **Baseline:** >10 lbs lost unintentionally in prior year
- **Grip strength:** Lowest 20% (by gender, body mass index)
- **“Exhaustion”** (self-report)
- **Walking time/15 feet:** Slowest 20% (by gender, height)
- **Kcals/week:** Lowest 20%
  - Males: <383 Kcals/week
  - Females: <270 Kcals/week

### C. Presence of Frailty

- **Positive for frailty phenotype:** ≥3 criteria present
- **Intermediate or prefrail:** 1 or 2 criteria present

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*Cardiovascular Health Study Measure* refers to the criteria used in the Cardiovascular Health Study to assess frailty. The criteria include weight loss, muscle mass loss, grip strength, physical activity, and walking speed.
HABC – 400 m walk performance and mobility limitation

Newman et al. JAMA; 2006;295:2018
HABC – 400 m walk performance and mortality

Newman et al. JAMA; 2006;295:2018
### Table 4. Adjusted 2004 Health Care Costs and Hospitalization Rates for Community-Dwelling Medicare Beneficiaries Aged 65 or Older by Self-Reported Ability to Walk 1/4 Mile (N=5493)*

<table>
<thead>
<tr>
<th>Ability to Walk 1/4 Mile</th>
<th>No Difficulty</th>
<th>Difficulty</th>
<th>Unable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean annual cost, in $1000 s†</td>
<td>9.51 (8.80-10.21)</td>
<td>12.28 (11.17-13.39)</td>
<td>13.42 (11.73-15.12)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-of-pocket</td>
<td>1.75 (1.60-1.91)</td>
<td>2.03 (1.79-2.26)</td>
<td>1.85 (1.61-2.10)</td>
</tr>
<tr>
<td>Hospitalizations per 100 persons†</td>
<td>25.1 (21.8-28.4)</td>
<td>39.2 (34.0-44.3)</td>
<td>47.3 (40.6-54.0)</td>
</tr>
</tbody>
</table>

Hardy et al. *J Gen Intern Med Online; 2010:Oct 23*
Predicted life expectancy by age and walking speed in men

Studenski et al. JAMA; 2011;305:50
Predicted life expectancy by age and walking speed in women

Studenski et al. JAMA; 2011;305:50
Interventions to maintain mobility

- ACE inhibitors
- Albuterol
- ARBs
- **Aspirin**
- Carnitine
- CoQ10
- Creatine
- Cytokine inhibitors
- DHEA
- Diet – high protein
- Diet – low calorie
- Erythropoietin
- Estrogens
- Growth hormone
- GH secretagogue
- Myostatin inhibitors
- NSAIDs
- Pentoxiphylline
- **Physical activity**
- Resveratrol
- SARMs
- Statins
- **Testosterone**
- Thalidomide
- **Vitamin D**
- Vitamin E
- Vitamin E
Fitness Arthritis and Seniors Trial - FAST

- **Health education**
  - n=149
  - p<0.001

- **Resistance exercise**
  - n=146
  - p<0.001

- **Aerobic exercise**
  - n=144
  - p=0.003

Ettinger et al. JAMA 1997;277:25
FAST - Incidence of ADL disability (a lot of difficulty or unable)

- Health education
  - n=80
  - p=0.02

- Resistance exercise
  - n=82
  - p=0.003

- Aerobic exercise
  - n=88
  - p=0.003

The LIFE Study
Pilot
Lifestyle Interventions for Independence in Elders
Successful aging intervention

- Organized health workshops relevant to older adults (e.g., healthful nutrition, how to effectively negotiate the health care system, how to travel safely, etc.)

- Short instructor-led program (5-10 min) of upper extremity stretching exercises
Physical activity intervention
Center-based in a group setting

- Aerobic (walking)
- Strength (lower extremities)
- Balance
- Flexibility stretching
- Behavioral counseling (group and telephone)
Frequency and duration

- Walking 3 to 6 days per week. (minimum walking bout 10 minutes with goal of 30 minutes per bout)
- Strength training 3 times per week (10 minutes per session)
Intensity: moderate

• Walking to be performed at “12 to 14” (somewhat hard) on Borg scale

• Strength training goal will be “15 to 16” (hard) on Borg scale
Aerobic

Wake Forest University

University of Florida
Aerobic

Stanford University

Outdoor walking

BP check

Taking a break during the walk
Resistance
Strength
Flexibility stretching
LIFE-Pilot - SPPB score

Means estimated from repeated measures ANCOVA adjusted for gender, field center and baseline values.

Pahor et al J Gerontol 2006;61:1157
Means estimated from repeated measures ANCOVA adjusted for gender, field center and baseline values.

LIFE-Pilot 400 m walk speed

Physical activity
Successful aging

LIFE-Pilot - Cumulative hazard mobility disability

Number at risk
- SA: 211
- PA: 213

Cumulative endpoints
- SA: 0
- PA: 0

Years since randomization
0.0
0.5
1.0
1.5

Cumulative Hazard
0.0
0.1
0.2
0.3

- Successful aging
- Physical activity

p=0.25
HR=0.74, 95%CI=[0.44, 1.24]

Effect of physical activity on frailty

Results from the LIFE-P study

Change in frailty prevalence

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Aging</td>
<td>25,5%</td>
<td>24,7%</td>
<td>23,2%</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>35,9%</td>
<td>17,6%</td>
<td>17,7%</td>
</tr>
</tbody>
</table>

Change in mean number of frailty criteria

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Aging</td>
<td>1,81</td>
<td>1,68</td>
<td>1,60</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>2,00</td>
<td>1,45</td>
<td>1,43</td>
</tr>
</tbody>
</table>

GLM - p

- Baseline: 0.001, 0.007
- Month 6: 0.001, 0.011
- Month 12: 0.001, 0.011
LIFE-P

Effect of the intervention on mean number of frailty criteria

Overall sample

Age <80 years old
Age ≥80 years old

Women
Men

Race: White
Race: Black
Race: Other

No frailty at the baseline
Frailty at the baseline

Number of diseases <3
Number of diseases ≥3

Mean difference of frailty score (SA-PA)
LIFE-P - Prevalence of frailty criteria at baseline, 6 mo and 12 mo visits, according to randomized groups

- Slow gait speed
- Low grip strength
- Sedentary
- Exhaustion
- Weight loss

P-values:
- Slow gait speed: P=0.26
- Low grip strength: P=0.94
- Sedentary: P=0.002
- Exhaustion: P=0.81
- Weight loss: P=0.19
Inflammation and Frailty in Older Women Enrolled in WHAS

Leng et al.
EPESE - IL-6 and 4 year incident mobility disability

- Probability

- Ln (IL-6)

- 2.5 pg/ml

- 95% CI

- Adjusted probability

- 95% CI

- n=633

Ferrucci et al JAGS 1999;47:639
<table>
<thead>
<tr>
<th>tertile</th>
<th>incidence</th>
<th>RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>22.2%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>26.9%</td>
<td>1.05</td>
<td>0.88-1.26</td>
</tr>
<tr>
<td>III</td>
<td>41.4%</td>
<td>1.40</td>
<td>1.18-1.68</td>
</tr>
<tr>
<td>I</td>
<td>19.8%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>30.6%</td>
<td>1.34</td>
<td>1.11-1.62</td>
</tr>
<tr>
<td>III</td>
<td>40.2%</td>
<td>1.65</td>
<td>1.37-1.98</td>
</tr>
<tr>
<td>I</td>
<td>25.0%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>28.7%</td>
<td>1.09</td>
<td>0.91-1.30</td>
</tr>
<tr>
<td>III</td>
<td>36.1%</td>
<td>1.18</td>
<td>0.99-1.41</td>
</tr>
</tbody>
</table>

*adjusted for age, gender, race, education, fat mass, smoking, CVD, COPD, diabetes, cancer, arthritis, NSAIDs, corticosteroids albumin, creatinine, EPESE perf.

Penninx et al JAGS 2004;52:1105
HABC - Composite measure of inflammation and RR of mobility disability

P-trend < .001

number of high inflammatory markers (upper tertile)

Penninx et al JAGS 2004;52:1105
LIFE-Pilot – Physical activity and IL-6

Nicklas et al. *JAGS; 2008;56:2045*
Fat accumulation within skeletal muscle is associated with muscle weakness and the loss of function in older adults.

The effects of physical activity on fat within muscle in older adults are not clear.

Goodpaster et al.  
*J Appl Physiol* 2008; 105:1498
LIFE-Pilot Muscle study

**Muscle size**
- N=20
- N=22

**Intermuscular adipose tissue**
- N=20
- P<0.05
- N=22

**Subcutaneous adipose tissue**
- N=20
- N=22

**Muscle quality**
- N=20
- N=22
- P<0.05
N = 1,600    -   average FU = 2.7 yrs Range 1.9-3.7 years
Lifestyle Interventions and Independence for Elders

- Design: Phase 3 RCT
- 1600 sedentary older persons who are at risk of disability, recruited at 8 sites
- Mean FU 2.7 years (min 1.9 - max 3.7 years)
- Intervention: aerobic + resistance exercise vs. health education
Outcomes

• **Primary outcome:** major mobility Disability defined as incapacity to walk 400 m

• **Secondary outcomes:**
  • ADL disability
  • Cognitive function
  • Injurious falls
  • Major mobility disability or death
  • Persistent major mobility disability
  • Cost-effectiveness

• **Tertiary outcomes:** cardiopulmonary events, dementia, MCI
LIFE Inclusion criteria

- 70-89 years
- Sedentary lifestyle (<20 min per week in structured PA, <150 min per week in moderate PA)
- Able to walk 400 m
- SPPB score ≤9 (45% ≤7)
- Gives informed consent, lives in the study area and does not plan to move
## Randomization Source

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brochure</td>
<td>31.2%</td>
</tr>
<tr>
<td>Letter</td>
<td>26.7%</td>
</tr>
<tr>
<td>Newspaper Ad</td>
<td>14.8%</td>
</tr>
<tr>
<td>Other (flyers, newsletters, Internet)</td>
<td>13.3%</td>
</tr>
<tr>
<td>TV Ad</td>
<td>3.9%</td>
</tr>
<tr>
<td>Referral</td>
<td>3.7%</td>
</tr>
<tr>
<td>Radio Ad</td>
<td>2.9%</td>
</tr>
<tr>
<td>Flyer</td>
<td>1.3%</td>
</tr>
<tr>
<td>Event</td>
<td>0.7%</td>
</tr>
<tr>
<td>Follow-up Call</td>
<td>0.4%</td>
</tr>
<tr>
<td>Magazine</td>
<td>0.1%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.0%</td>
</tr>
<tr>
<td>Method</td>
<td>Participants Randomized</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Brochures/letters</td>
<td>$658,849</td>
</tr>
<tr>
<td>Events</td>
<td>$47,779</td>
</tr>
<tr>
<td>Print ads</td>
<td>$275,335</td>
</tr>
<tr>
<td>TV and radio</td>
<td>$355,113</td>
</tr>
<tr>
<td>Other (flyers, newsletters, Internet)</td>
<td>$37,135</td>
</tr>
<tr>
<td>Referral</td>
<td>60</td>
</tr>
<tr>
<td>Don't Know/Refused</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$1,374,213</strong></td>
</tr>
</tbody>
</table>
## Adherence
### Attendance to center-based interventions

<table>
<thead>
<tr>
<th></th>
<th>25&lt;sup&gt;th&lt;/sup&gt;%</th>
<th>Median</th>
<th>75&lt;sup&gt;th&lt;/sup&gt; %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Aging</td>
<td>73</td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>60</td>
<td>76</td>
<td>90</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>78.9 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>67.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>30.2 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPB score</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 m walk time</td>
<td>8.5 min (speed=0.78 m/sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>70.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>7.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>6.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>4.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>15.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>22.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sample Collection/Processing
- 1635 Participants recruited at 8 sites across the country.
  - Timepoints for blood samples (serum, EDTA-plasma, Citrated-plasma, Heparin-plasma)
    - Baseline
    - 6 months [4 of the 8 sites or 800 participants]
    - 12 months
    - 24 months
  - Timepoints for urine samples
    - Baseline
    - 12-month
    - 24-month
  - Timepoints for DNA samples
    - 12-month only
LIFE Timeline

• Feb 2010    Start randomization
• Nov 2011   n=1600 goal reached
• Dec 2011   n=1635 randomization complete
• Summer 2012 Release of baseline data
• Nov 15 2013 Follow-up complete
• May 2014    Presentation of main results
• Summer 2014 Release of follow-up data
Conclusions

• Observational studies and small randomized controlled trials support the view that regular physical activity prevents the onset and progression of disability and frailty.

• Reduction of inflammation and sarcopenia are potential beneficial mechanisms.

• Definitive evidence from large Phase 3 randomized controlled trials is pending.
Conclusions

• In LIFE-P physical activity reduced the progression of frailty primarily by reducing sedentariness. A larger sample size would be needed to detect a significant impact on the other frailty criteria.

• Interventions that specifically target a single criterion of frailty can avert the progression of frailty.

• Multimodal interventions that target multiple criteria of frailty are likely the most effective approach for the prevention of frailty.