Frailty conundrums: dilemmas and unsolved conceptual issues.

WHO: Frailty Network Meeting
Geneva, Switzerland Nov 2016
Disclosures:

• **Consultancies:** Merck, Eli Lilly, Essentient, Regeneron, Dairy Management Inc., Nestle’ Inc.

• **Advisory board memberships:** Cytokinetics, Segterra, Aging in Motion, Myosyntax, Ammonett.

• **Grant support:** NIH (NIA, NHLBI, NIDDK), USDA, Department of Defense, Dairy Research Institute, Unilever, Nestle’ Inc., Regeneron.
Skeletal Muscle Matters!

- Makes up 45-50% of body mass
- Fundamental role in locomotion, $O_2$ consumption, whole-body energy metabolism, and substrate turnover and storage
- Secretory organ (myokines)
- Robust skeletal muscle is a central factor in whole-body health and essential for maintaining energy homeostasis

Mobility across species

Dickinson et al.  
*Science* 2000; 288:5463
Aging drosophila and performance

Miller et al. *Biophys J* 2008;95:2391
HABC – 400 m walk performance and mortality

Newman et al. *JAMA*; 2006;295:2018
Sarcopenia: Age-associated loss in muscle mass and function

Female 70 yrs.
BMI = 23.3

Female 85 yrs.
BMI = 24.6

Sarcopenia is a key biological component of the frailty syndrome
Historic Alignment Worldwide of Societal, Governmental, and Pharmaceutical Industry Interest in Sarcopenia:

• Recognized priority area of research by NIA: NIA-PCORI Initiative STRIDE Study, LIFE Study.

• IMI EU initiative: SPRINT-T Trial.

• Increased international awareness of Sarcopenia: WCO, IFSCR.

• Multiple candidate molecules in early and mid-stage development targeting skeletal muscle dysfunction, sarcopenia, and ultimately frailty.

• October 2016 establishment of ICD-10 for Sarcopenia.
Behavioral Interventions to target Frailty
**Frailty**

Frailty is a state of increased vulnerability to stressor events conferring high risk for major negative outcomes, including disability, falls, fractures and mortality.

Consensus on its operationalization has not yet been achieved.

Most widely used definition operationalized by Fried et al. is phenotypic frailty, validated in the CHS study, with the presence of ≥3 of 5 criteria denoting frailty:

*(weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength)*

Clegg et al. Lancet 2013  
Keevil et al. Proc Nutr Soc 2015  
Simpler tool validated using data from the SOF study ➔ the SOF frailty index, with the presence of ≥2 criteria of 3 denoting frailty (weight loss, inability to rise from a chair 5 times without using arms, and self-reported reduced energy level)

Predict risk of disability, falls, fracture, and mortality as well as the more complex Fried frailty index

SOF frailty index does not integrate the level of physical activity, making this tool potentially more meaningful for the evaluation of physical activity-based interventions

Lifestyle Interventions and Independence for Elders*

• Design: a Phase 3 RCT (LIFE-M)
• N = 1600 (8 clinical centers)
• Mean FU: 2.7 years (min 1.9 - max 3.9 years)
• Intervention: aerobic + resistance exercise vs. health education

*Fielding et al. J. Gerontol. 2011
Inclusion criteria

- Age 70-89 yrs
- Sedentary
- Able to walk 400 m
- SPPB score $\leq 9$ (45% $\leq 7$)
Major Mobility Disability

HR = 0.82, 95% CI = 0.69 - 0.98
p = 0.03

Physical activity

Health Education

Pahor et al JAMA 2014
## Baseline Characteristics of Participants by Randomization Groups and Frailty Status

Frail according to Fried index: 26.9% (439/1635)
Frail according to SOF index: 19.6% (321/1635)

<table>
<thead>
<tr>
<th></th>
<th>Physical activity (n=818)</th>
<th></th>
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<th>Health education (n=817)</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Frail (n=222)</td>
<td>Not frail (n=596)</td>
<td>All</td>
<td>P Value</td>
<td>Frail (n=217)</td>
<td>Not frail (n=600)</td>
<td>All</td>
<td>P Value</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>79.9 ± 5.4</td>
<td>78.2 ± 5.1</td>
<td>78.7 ± 5.2</td>
<td>&lt;0.001</td>
<td>80.4 ± 5.3</td>
<td>78.6 ± 5.1</td>
<td>79.1 ± 5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>165 (74%)</td>
<td>382 (64%)</td>
<td>547 (67%)</td>
<td>0.006</td>
<td>169 (78%)</td>
<td>382 (64%)</td>
<td>551 (67%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean (SD) 3MSE, score</td>
<td>90.8 ± 5.7</td>
<td>91.8 ± 5.4</td>
<td>91.5 ± 5.5</td>
<td>0.020</td>
<td>90.7 ± 5.5</td>
<td>92.0 ± 5.2</td>
<td>91.6 ± 5.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean (SD) CES-D, score</td>
<td>12.4 ± 9.3</td>
<td>6.9 ± 6.5</td>
<td>8.3 ± 7.7</td>
<td>&lt;0.001</td>
<td>12.4 ± 8.8</td>
<td>7.6 ± 7.2</td>
<td>8.8 ± 7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD) number of chronic conditions</td>
<td>1.9 ± 1.2</td>
<td>1.7 ± 1.1</td>
<td>1.8 ± 1.1</td>
<td>0.028</td>
<td>2.1 ± 1.2</td>
<td>1.8 ± 1.1</td>
<td>1.8 ± 1.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean (SD) SPPB, score</td>
<td>6.7 ± 1.8</td>
<td>7.7 ± 1.4</td>
<td>7.4 ± 1.6</td>
<td>&lt;0.001</td>
<td>6.3 ± 1.7</td>
<td>7.7 ± 1.4</td>
<td>7.3 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD) number of Fried frailty index criteria</td>
<td>3.3 ± 0.5</td>
<td>1.4 ± 0.7</td>
<td>1.9 ± 1.0</td>
<td>&lt;0.001</td>
<td>3.2 ± 0.4</td>
<td>1.4 ± 0.7</td>
<td>1.9 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Frail vs not frail subjects within group of randomization
### Incidence of First Initial Frailty

**According to Randomization Group at Each Visit**

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<tr>
<td><strong>Fried frailty index</strong></td>
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<tr>
<td>Baseline prevalence of frailty</td>
<td>222 (0.27) [0.24-0.30]</td>
<td>217 (0.27) [0.24-0.30]</td>
</tr>
<tr>
<td>Baseline prevalence of not frailty</td>
<td>596 (0.73) [0.70-0.76]</td>
<td>600 (0.73) [0.70-0.77]</td>
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<tr>
<td><strong>Cumulative incidence</strong></td>
<td></td>
<td></td>
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<tr>
<td>6 Month</td>
<td>54 (0.18) [0.13-0.23]</td>
<td>73 (0.24) [0.19-0.30]</td>
</tr>
<tr>
<td>12 Month</td>
<td>109 (0.20) [0.16-0.23]</td>
<td>125 (0.22) [0.19-0.26]</td>
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<tr>
<td>24 Month</td>
<td>154 (0.15) [0.13-0.18]</td>
<td>177 (0.18) [0.15-0.20]</td>
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<tr>
<td><strong>SOF frailty index</strong></td>
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<tr>
<td>Baseline prevalence of frailty</td>
<td>159 (0.19) [0.17-0.22]</td>
<td>162 (0.20) [0.17-0.23]</td>
</tr>
<tr>
<td>Baseline prevalence of not frailty</td>
<td>659 (0.81) [0.78-0.83]</td>
<td>655 (0.80) [0.77-0.83]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative incidence</strong></td>
<td></td>
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</tr>
<tr>
<td>6 Month</td>
<td>71 (0.22) [0.17-0.27]</td>
<td>102 (0.31) [0.25-0.37]</td>
</tr>
<tr>
<td>12 Month</td>
<td>127 (0.21) [0.17-0.24]</td>
<td>138 (0.23) [0.19-0.27]</td>
</tr>
<tr>
<td>24 Month</td>
<td>177 (0.16) [0.14-0.19]</td>
<td>195 (0.18) [0.15-0.20]</td>
</tr>
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</table>

Data are presented as n (count/person year) [95% CI for incidence]
## GEE Models Predicting Frailty Over 24 Months According to Randomization Group

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted odds ratio (95% CI)</th>
<th><em>P</em> Value</th>
<th>Adjusted odds ratio* (95% CI)</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried frailty index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity (n=818)</td>
<td>0.83 [0.69-0.99]</td>
<td>0.040</td>
<td>0.81 [0.68-0.98]</td>
<td>0.028</td>
</tr>
<tr>
<td>Health education (n=817) (Reference)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SOF frailty index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity (n=818)</td>
<td>0.81 [0.67-0.98]</td>
<td>0.034</td>
<td>0.86 [0.71-1.04]</td>
<td>0.125</td>
</tr>
<tr>
<td>Health education (n=817) (Reference)</td>
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</table>

* Baseline value of the outcome, gender and field center (both used to stratify randomization), age, intervention, clinic visit, and intervention-by-visit interaction included in the models.
Estimated Effects of the Intervention on the Mean Number of Fried Frailty Criteria

![Graph showing the mean number of frailty criteria over time with significant decreases after the intervention. The graph includes data points at baseline, month 6, month 12, and month 24. The average effect is indicated as P<0.001.]
Major mobility disability and persistent major mobility disability occurrence in frail participants at baseline

**Major mobility disability**

\[ HR = 0.69 \ [CI, \ 0.49-0.98]; \ P = 0.04 \]

**Persistent mobility disability**

\[ HR = 0.58 \ [CI, \ 0.39-0.91]; \ P = 0.01 \]

Overall, the interaction term between frailty and randomization arm was not significant for major mobility disability outcome \( (P=0.31) \).
Summary:

- Age-associated skeletal muscle dysfunction (Sarcopenia) is a key biological mediator of the frailty syndrome.

- 24 months of a structured, moderate-intensity physical activity program significantly reduced the risk and severity of frailty.

- Among frail individuals, the risk of major mobility disability was reduced by 31% with the physical activity intervention, while falls and fractures risks were not modified. These results stress the need to engage even the more frail individuals in such programs.

- Function promoting anabolic therapies should be evaluated with respect to their efficacy in both non-frail and frail older adults.
The Disablement Pathway*, Intrinsic Capacity, Frailty, and Sarcopenia

Pathology: reduced muscle size, neural activation/recruitment, mitochondrial function, local vascular change

Impairment: muscle strength/power, aerobic/endurance capacity

Functional Limitation*: gait speed, chair rise time

Disability*: role limitations

Dietary, physical activity, pharmacologic interventions

Intrinsic Capacity

Functional Ability

*Nagi, 1965; Verbrugge & Jette, 1994
Fig. 1. Components of frailty. *(Adapted from* Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiologic dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci* 2009;64(10):1050; with permission.*)