Frailty and resilience in aging

Linda P. Fried, MD, MPH
Why...

- Are some older adults
  - At risk for adverse health outcomes
  - Resilient in the face of stressors...
- And others not?
- Do we “know it when we see it”? 
Frailty: Geriatricians’ Perspective

- Aging-related state of vulnerability
- Thought recognizable clinically
- High risk - for: mortality; falls; disability; hospitalization
- Potential for treatment and prevention of frailty as well as its poor outcomes
The patient’s illness:

- Contributors to health outcomes:
  - The disease
  - The *underlying* health status and vulnerability
Frailty: Definition of Clinical Syndrome

- Syndrome of shrinking, slowing and weakness, with low activity and low energy
Fried & Walston, 1998

Cycle of Frailty

Chronic Undernutrition

Neuroendocrine Dysregulation
Anorexia of aging

Aging: Senescent musculoskeletal changes
Negative Energy Balance
Negative Nitrogen Balance
Weight Loss

Total Energy Expenditure
Activity
Walking Speed

Resting Metabolic Rate

Strength & Power

Immobilization
Impaired balance
Falls and Injuries

Insulin sensitivity
Osteopenia

Loss of muscle mass

Sarcopenia

VO₂max
Hypothesized Vicious Cycle of Energy Dysregulation

Fried, 1998; 2001
Formalized phenotype:
Definition and validation of the clinical syndrome of frailty

Multiple (3-5/5) criteria present = frail:
• Weight loss
• Weakness
• Exhaustion
• Slowed walking speed
• Low activity

Frailty phenotype is consistent with definition of a syndrome

1. No tendency for distinct subsets of items to aggregate in different classes

2. Rather, stepwise progression in prevalence of each criterion across classes, consistent with overall aggregation

Bandeen-Rouche, J Ger Med Sci 2006
Frailty: Validation that the whole is greater than the sum of the parts

- Criterion and construct validity (Fried, 2001; Bandeen-Roche 2006)
- Validation as a syndrome (Bandeen-Roche, 2006)
- Aggregate phenotype predicted mobility disability and other outcomes better than any 1 or 2 markers – such as walking speed, strength, weight loss
- Cross-validation in multiple studies
Frailty is chronic and progressive:
Early, preclinical frailty predicts onset of frailty over 3 years

- Unadjusted: O.R. = 4.51 (p < .0001)
- Adjusted: O.R. = 2.63 (p < .0001)

Cardiovascular Health Study Fried et al, 2001
Spectrum of resilience and frailty in older adults

A:
- Resilient;
- Not frail

B:
- Prefrail;
- Vulnerable;
- Poor recovery
- Decompensates with minor external stress.
- Onset of frailty

C:
- Frailty Syndrome;
- Outcomes:
  - Loss of independence

D:
- Endstage frailty/predeath
Theoretical Progression of Frailty

Fried 2000
Clinical Presentation

- Weight Loss
- Sarcopenia

Physiologic Vulnerability

- ↓ physical activity
- ↓ Motor performance
- ↓ Strength
- Exhaustion/
- ↓ exercise tolerance

Physiologic Dysregulation

Cellular Function, Molecular and Genetic Characteristics

Fried LP, SAGE-KE, 2005
Dysregulation/deficits of multiple physiologic systems associated with frailty

- Sarcopenia
- Inflammation
- Decreased heart rate variability
- Altered clotting processes
- Anemia
- Altered hormones: Insulin resistance, ghrelin, resistin, DHEAS, IGF1, cortisol
- Micronutrient, protein, energy deficiencies
Number of Systems Abnormal & Frailty

Combined WHAS I and WHAS II (Age 70-79)

Fried, Xue et al
Evidence for Nonlinearity of Relationship of Number of Systems Abnormal with Frailty

Fried et al 2008
Biology associated with frailty

• Dysregulation of multiple physiologic systems associated with phenotype
• Non linear relationship
• Threshold: Frailty is an emergent property - of dysregulated complex adaptive system
Frailty: dysregulation of the nonlinear, complex adaptive system that maintains a resilient and robust human organism

*Biologic changes of aging as the drivers*
Components of complex dynamical systems

• Dysfunction of physiologic systems = modules
• Loss of physiological networking, mutual regulation, redundancy
• Loss of reserves – within and across modules
• Decreased homeostatic regulation
• Likely contributes to both phenotype of frailty and vulnerability to stressors
Dysregulation under steady state conditions
Mean diurnal profiles of cortisol during a 24-hour period

System control & redundancy:
Multisystem Dysregulation and Interactions May Underlie Loss of Reserves, Frailty

- Multisystem Dysregulation
- Interactions
- Loss of Reserves, Frailty

Compensatory Mechanisms:
- Glucose intolerance
- SNS activity
- Hematopoiesis
- Inflammation
- Mitochondrial dysfunction
- Altered cellular metabolism
- Cellular senescence
- DNA damage
- Free radicals
- Altered hormones

Genetic Variation

Physiologic

Molecular Genetic
Complex System: Network Dynamics Under Conditions of Challenge
GTT: Altered Glucose-Insulin Dynamics in Frailty

Kalyani et al, JGMA, 2011
Magnetic Resonance Spectroscopy evaluation of frail v. nonfrail: Phosphocreatine response, muscle

Time for PCR levels to recover to 95% of its baseline value following a 30-second isometric plantarflexion exercise.
Time to recovery of PCr following a 30-second isometric plantarflexion exercise, MRS, women 85-95 years

Varadhan R et al, in preparation
Frailty Syndrome: Modal Pathway, 2013

**Molecular & Genetic**
- E
- Mitoch
- Genes
- Epigenetic
- Telomere

**Physiology**
- Many systems ↑ or ↓ in parallel
- Synergistic and nonlinear risk
- Complex systems unraveled

**Syndrome**
- Critical mass:
- Weakness
- Weight loss
- Slowed performance
- Exhaustion
- Low activity

**Outcomes**
- Falls
- Disability
- Hospital/surgical
- Death

Disease

Fried et al, 2001; Bandeen-Roche 2006, Walston et al, 2002; Chaves 2006; Leng et al, 2002, 2004; Cappola 2003; Semba 2006; Varadhan 2007; Fried 2009
Frailty syndrome: associated with threshold severity of multisystem dysregulation
Frailty as the emergent property of a dysregulated complex adaptive system
Homeostatic Mechanisms and Frailty: Loss of resilience with aging

Xue, Varadhan
Ultimately, successful prevention or treatment of frailty will involve intervening on the systems biology
Weight Loss
Sarcopenia
↓ Strength
Exhaustion
↓ Motor performance
↓ physical activity

Clinical Presentation of Physical Frailty

↓ Inflammation
↑ Inflammation

Physiologic Dysregulation

↓ Hormones
↓ HRV

Molecular and Genetic Characteristics

↑ Free radicals

Mitochondrial Dysfunction

DNA damage

Cellular Senescence

Altered cellular metabolism

Genetic variation

CNS

Immune Modulations

Hemoglobin
### Phenotype of Frailty

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CHS Study Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrinking</td>
<td>BL: Unintentional weight loss &gt;10 lbs F/U: ≥ 5% weight loss over one year</td>
</tr>
<tr>
<td>Weakness</td>
<td>Grip strength: lowest 20%</td>
</tr>
<tr>
<td>Poor endurance</td>
<td>Exhaustion (self-report)</td>
</tr>
<tr>
<td>Slowness</td>
<td>Walking time: lowest 20%</td>
</tr>
<tr>
<td>Low activity</td>
<td>Kcal/week : lowest 20%</td>
</tr>
</tbody>
</table>

**Non-frail:** 0/5  
**Pre-frail:** 1 or 2/5  
**Frail:** 3, 4, or 5/5

Frailty 2013: a clinical syndrome

A consensus group of delegates from 6 major international, European, and US societies agreed:

“Physical frailty is an important medical syndrome”.

Defined as “A clinical state....of increased vulnerability to developing dependency and/or mortality when exposed to a stressor.”

“All persons over 70 years should be screened”

Morley J et al, JAMDA, 2013
Frailty Prevalence: ≥3 criteria present, Cardiovascular Health Study

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total %</th>
<th>Women % (n=2710)</th>
<th>Men % (n=2025)</th>
</tr>
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<tbody>
<tr>
<td>65-70</td>
<td>3.2</td>
<td>3.0</td>
<td>1.6</td>
</tr>
<tr>
<td>71-74</td>
<td>5.3</td>
<td>6.7</td>
<td>2.9</td>
</tr>
<tr>
<td>75-79</td>
<td>9.5</td>
<td>11.5</td>
<td>5.5</td>
</tr>
<tr>
<td>80-84</td>
<td>16.3</td>
<td>16.3</td>
<td>14.2</td>
</tr>
<tr>
<td>85-89</td>
<td>25.7</td>
<td>31.3</td>
<td>15.5</td>
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<tr>
<td>90+</td>
<td>23.1</td>
<td>12.5</td>
<td>36.8</td>
</tr>
<tr>
<td>Total</td>
<td>6.9</td>
<td>7.3</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Frail older adults: Highly vulnerable subset

• Clinically at risk – independent of diseases, for:
  – Mortality
  – Falls
  – Disability, Dependency
  – Delayed and incomplete recovery
  – Adverse outcomes of hospitalization, surgery

Fried 2001; Bandeen-Roche 2006; Boyd 2006; Makary 2011
Frailty, as defined, validated in U.S. community-dwelling cohorts as meeting definition of clinical syndrome

- *Cardiovascular Health Study (CHS)*: men and women 65-101 years at baseline
- *Women’s Health and Aging Studies I & II (WHAS)* combined: women 70-79 years:
  - WHAS I: 1/3 most disabled
  - WHAS II: 2/3’s least disabled

Fried LP et al, J Ger Med Sci, 2001; Bandeen-Roche et al 2006
Significance of frailty as a phenotype of aging

• Marker (independent of disease) of vulnerability:
  – Predictor of disability, mortality and risk
  – Predictor of poor recovery from stressors
  – Dose response of risk at different levels of severity
  – Impact on same outcomes as specific diseases

• Chronic, progressive
  – Initial presentations: muscle weakness, slowness, low PA
  – Preclinical predicts clinical frailty
  – Early stages likely most responsive to intervention
  – End stage: high risk for mortality

• Primary v. secondary frailty

• Distinctive underlying biology of multisystem dysregulation
Behavioral predictors of frailty: Clues to Prevention and Treatment

• Low physical activity
• Loss of muscle mass
• Smoking
• Dietary intake:
  – Low energy intake: ≤21kcal/kg
  – Low protein intake
  – Low serum micronutrients: carotenoids, Vitamin D, E, folate;
  – ≥3 nutritional deficiencies

Fried 2001; Bartali 2006; Semba 2006
C-Reactive Protein and Frailty, Cardiovascular Health Study

Not Frail (N=2285)
2.7 ± 4.0 ng/ml

Intermediate (N=2141)
3.7 ± 6.5 ng/ml

Frail (N=299)
5.5 ± 9.8* ng/ml

* different from not frail (p ≤ 0.001)

Walston J, et al. Archives of Internal Medicine, 2002
Dose response associations with graded categories of frailty

Leng, unpublished
Association of Number of Nutrient Deficiencies With Incidence of Frailty, WHAS I & WHAS II

Semba et al, 2005
Number of Abnormal Hormones by Frailty Status

Cappola et al 2008
Experimental evaluation of dynamical systems’ dysregulation underlying frailty

• Challenge tests of frail, prefrail and nonfrail 85-95 y/o women (WHAS II) to test:
  – Observation: Stressor reveals underlying dysregulation in discrete physiologic systems in frail
  – Implications: energy dysregulation driving generalized phenomenon of multi system dysregulation in frailty
Women’s Health and Aging Study II

• Prospective, observational cohort study of women 70-79 years in 1994
• Selected to be representative at baseline of the 2/3’s least disabled women 70-79 in community
• Followed every 18-36 months for 15 years
• In 2005-7, underwent experimental evaluations in their homes or JHU (MRS)
Theories evaluated in our studies of women 85-95 years

• Physiologic dysregulation in frailty more notable in stressed state, demonstrating, in multiple systems:
  – Delayed, exaggerated and prolonged responses, and delayed recovery to baseline, relative to nonfrail and prefrail
  – Increased variance in responses
Challenge tests of physiologic stressors in 85-95 year old women living in community

• Phenotype: Frail, prefrail and nonfrail
• Challenge tests across a range of systems included:
  – **GTT**: Glucose and insulin response (over 180 minutes)
  – **ACTH stim test**: cortisol and DHEA response (over 120 minutes) to 250 ug ACTH
  – **MRS of tibialis anterior**: PCr response re: energy utilization and repletion in muscle with 30-sec isometric plantarflexion exercise
  – **Flu shot**: Ab response to in vivo stimulation with standard 2007 trivalent inactivated influenza vaccine (women and men, 72-95)
Flu shot challenge: Seroconversion rates to influenza H1N1, H3N2, and B vaccine strains in frail and non-frail older adults

Strains

H1N1

Rates of seroconversion (%) in response to influenza immunization (4-fold or higher increase in H1 titers)

H3N2

B

Leng, unpublished
GTT response in frail v. non frail

• Fasting glucose did not vary by frailty status;
• At 120 mins: glucose levels of frail 67mg/dL higher (adjusting for age, BMI)
• Evidence of delayed, exaggerated and prolonged recovery for frail post glucose load
• Frail response to GTT c/w dysregulation, decreased complexity and balance of dynamical system (Not shown):
  – Elevations in glucose raising hormones
  – Lowered glucose lowering hormones
Proposed model for relationship of frailty status with circulating levels of energy metabolism hormones in the basal state

- **Inflammation:** ↑ IL-6
- **Growth Hormone Axis:** ↑ GH resistance, ↓ IGF-1
- **Insulin Resistance**
- **Energy Imbalance**
- **Sarcopenia**
- **Physical exhaustion**
- **↓ Appetite / Weight Loss**
- **Adipocyte hormones:** ↑ leptin resistance, ↑ resistin, ↓ adiponectin
- **Gut hormones:** ↓ ghrelin, ↓ GLP-1
Predominance of glucose dysregulation, 84-95 year old women without diabetes, WHAS

- In OGTT substudy, only 27% had normal fasting glucose (<100mg/dL) and normal GTT.
- 48% had prediabetes: impaired fasting glucose, impaired glucose tolerance or both;
- 25% had undiagnosed diabetes.
- Prediabetes and diabetes due to abnormal OGTT in 71 and 78%, respectively.
Frailty evidence: dysregulation of a complex, dynamical and adaptive system

- **Submodules of the system** essential to optimal regulation for a robust system – and hide regulatory complexity: eg: intracellular signaling cascades and transcriptional pathways that regulate inflammation in aging; metabolic: cortisol, glucose, SNS, RMR (increased variability for frail)
- **Interconnectedness, redundancy and complex regulatory responses** – within and across modules – that maintains tight homeostatic balance in face of stressors
- Frailty is an **emergent property of nonlinear dynamics**; nonlinearity of multisystem dysregulation, with loss of resilience, robustness and ability to compensate for stressors past a threshold
- **Consequence:** Compromised ability to adapt to stressors (consistent with Lipsitz and Goldberger, 1992 and 2002): decreased physiologic complexity with maladaptive response to perturbations, impaired homeostatic control; network structure and dynamics revealed under conditions of stress
Ho: Systems Biology of Resilience…Frailty

• Optimal regulation essential for a robust systems

• Complex pathways:
  – Network structure: interactions
  – Network dynamics: under various conditions
  – Redundancy and mechanisms to minimize malfunction

Core hypothesis: *dysregulated energetics associated with aging*

Would lead to a generalized phenomenon and phenotype
Mitochondrial DNA Control Region and Frailty in older adults

• Study of 4,459 men and women in CHS
• mt204C allele associated with greater likelihood of frailty (adj OR = 2.04, p = .02), lower grip strength (adj coeff = -2.04, p = .002)
• Supports role for mitochondrial genetic variation in frail and later life muscle strength

Moore AZ...Arking, PLoS One 2010
Biologic drivers of multisystem dysregulation underlying frailty?

• Mitochondrial dysfunction?
• Cellular senescence?
• Altered intercellular communication?
• Loss of proteostasis?
• Deregulated nutrient sensing?
• Genomic instability?
• Telomere attrition?
• Epigenetic alterations?
• Stem cell exhaustion?

– Hallmarks of Aging (from Lopez-Otin et al, 2013)
Implications

• Science
• Methods of science
Frailty syndrome: potential clinical applications

• Diagnosis
• Screening
• Prognosis
• Prevention
• Treatment, both for frailty and of other diseases because frailty present
• Management and goal setting
• Palliative care and hospice eligibility
The Punchlines, Implications

• Frail older adults: Low resilience, high risk
• Moments of risk matter
• Early prevention likely to be most successful; prevent emergent property
  – Biologic drivers and multifactorial interventions will be model for prevention; nutrition and physical activity are models
  – Screening should be useful
• Late: tertiary prevention, palliative care and extrinsic compensations matter
Multisystemic syndrome; single replacement therapies unlikely to be effective
Natural History of Investigation

7/1. The Genesis and Rationale:
Clinical Problem

2. Conceptual Framework:
Population-based and Clinical Evidence

6. Ultimate Causes:
Genetics – Environment
Laboratory ↔ Populations
-- Modifiable Pathways --

5. Subclinical Components and Mechanisms:
Hypothesis testing;
Modifiable Pathways
Population ↔ Laboratory

4. Converging Literature:
Hypotheses development
- Physiology: subclinical components and mechanisms
- Biology: Ultimate cause

3. Phenotype:
Clinically observable syndrome
- Population-based evidence
- Modifiable pathways

Clinical Trials
Acknowledgments

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Roles of Epidemiology in the Cycle of Investigation

• Import of condition
• Define clinical presentation/phenotype
• Risk factors: Independent
• Multisystem risk factors
• Defining the “systems biology”: relating dysregulation across multiple physiology to both clinical presentation and underlying cellular and genetic processes.
• Translation:
  – From one level of investigation to the next
  – Back to humans through identification and testing of interventions
Primary v. secondary frailty

- Age-related
- Associated with inflammatory diseases: HIV, CHF, COPD, Diabetes, Obesity
- Implications: final common pathway of loss of resilience and reserves
Frailty syndrome is associated with chronic diseases

• Diseases independently associated:
  – CVD:
    • Clinical CHF, MI, Angina, Claudication, Stroke, Hypertension
    • Subclinical CVD: carotid stenosis, wall thickness; ECG abnormalities
  – COPD
  – Anemia
  – Cancers
  – Diabetes
  – Metabolic syndrome
  – HIV
  – Chronic kidney
  – Rheumatoid arthritis
  – Late life Depression
• Inflammatory disease count a/w frailty: OR= 1.84
• Synergistic interactions: COPD*anemia; depression*anemia; anemia*CVD; CVD* COPD
Mean maximal internal carotid wall thickness by CVD and frailty status

Frailty syndrome appears to be a final common pathway for catabolic diseases as well as aging related emergent property.

*Potential mechanism for association of frailty with chronic disease*
Frailty and chronic disease interact in shared outcomes

• Frailty increases mortality risk of disease: preceding AIDS increases mortality risk (MACS study; Desquilbet et al); CHF

• Risk of disability: at least additive, chronic diseases and frailty

• Frailty predicts poorer outcomes from interventions for disease: from surgery for disease (Makary) and from hospitalization (Boyd) for disease
Shared risk factors for frailty and chronic diseases

e.g., Inflammation
Insulin resistance
Mechanistic link between frailty and cardiovascular disease

Aging process
- Lifelong antigen exposure
- Redox imbalance
- Angiotensin 1R activation
- Obesity / insulin resistance

Chronic low-grade inflammation

Frailty

Cardiovascular disease

Adverse outcomes
- Morbidity / complications
- Progression to disability
- Institutionalization
- Death

Aging-related changes of frailty could drive disease development

Examples:
- Chronic, low grade inflammation
- Metabolic dysregulation
Could frailty be part of a shared continuum with endorgan disease?

• Where does dysregulation (eg: glucose intolerance with aging) slide into being a disease (eg: diabetes)?
Relationships of causes of frailty with those of clinical, end-organ disease

• Shared causes for distinct phenotypes:
  – Physiologic: eg, inflammation, metabolic homeostasis, fat: muscle;
  – Biologic: eg, mitochondrial dysfunction, energy production, transcription factors (eg, NF-kB), free radicals from oxidative stress, AGEs, cellular senescence
Does differentiating frailty and chronic diseases matter?

• Thinking about effective prevention or treatment: considering frailty as an emergent property of a dysregulated complex system may open some insights and goals
  – Single target intervention may not be effective unless effect amplified across many downstream systems
  • Examples: physical activity and diet
  – When frailty-related dysregulation is severe enough, disease treatment may not be useful
Many modifiers of frailty with aging

- Multimorbid diseases
- Medications
- Physical activity
- Dietary intake;
  - Taste and smell: salt, bitter and sour detected by only 30-50% of older women at low strength (WHAS II; in preparation)
  - Access to food, due to disability, neighborhood, poverty
  - Social isolation, depression
Association of adherence to a Mediterranean-style diet and the odds of frailty and its components\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Frailty and its components</th>
<th>Age, sex adjusted, OR (95% CI)</th>
<th>Multivariate, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling of exhaustion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Medium</td>
<td>0.96 (0.66, 1.39)</td>
<td>0.94 (0.63, 1.41)</td>
</tr>
<tr>
<td>High</td>
<td>0.69 (0.45, 1.07)</td>
<td>0.73 (0.45, 1.16)</td>
</tr>
<tr>
<td>Low physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Medium</td>
<td>0.66 (0.46, 0.95)</td>
<td>0.69 (0.47, 1.01)</td>
</tr>
<tr>
<td>High</td>
<td>0.58 (0.39, 0.88)</td>
<td>0.62 (0.40, 0.96)</td>
</tr>
<tr>
<td>Poor muscle strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Medium</td>
<td>1.14 (0.73, 1.79)</td>
<td>1.09 (0.69, 1.73)</td>
</tr>
<tr>
<td>High</td>
<td>0.85 (0.51, 1.43)</td>
<td>0.82 (0.48, 1.40)</td>
</tr>
<tr>
<td>Low walking speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Medium</td>
<td>0.85 (0.54, 1.34)</td>
<td>0.85 (0.53, 1.37)</td>
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<tr>
<td>High</td>
<td>0.47 (0.27, 0.81)</td>
<td>0.48 (0.27, 0.86)</td>
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<tr>
<td>Frailty</td>
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<tr>
<td>Low</td>
<td>1.00</td>
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<tr>
<td>Medium</td>
<td>0.60 (0.34, 1.06)</td>
<td>0.71 (0.42, 1.21)</td>
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<tr>
<td>High</td>
<td>0.26 (0.11, 0.59)</td>
<td>0.30 (0.14, 0.66)</td>
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</table>

\textsuperscript{1} Multivariate model: adjusted for age (y), sex, energy intake (kcal/d), status of frailty (or its components) at previous examinations, BMI (kg/m\textsuperscript{2}), education (y), MMSE score, current smoker (Y/N), and presence of chronic diseases (Y/N). InCHIANTI, Invecchiare in Chianti; MDS, Mediterranean Diet Score; MMSE, Mini Mental State Examination.

\textsuperscript{2} MDS scores for categories: low, \( \leq 3 \); medium, 4-5; high, \( \geq 6 \).

Talegawkar SA, Bandinelli S, et al. (2012)
WHO/IOM Pathway to Disability

Pathology/
Disease → Impairments → Functional Limitations → Disability → Frailty
### Number of Criteria for Frailty Associated with Risk of ADL Dependency

<table>
<thead>
<tr>
<th># Criteria</th>
<th>Incidence/100 P-Y</th>
<th>H R unadj</th>
<th>H R adjusted</th>
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<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>1</td>
<td>12</td>
<td>1.54</td>
<td>1.33</td>
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<tr>
<td>2</td>
<td>17</td>
<td>2.21 *</td>
<td>1.62 *</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>3.40 *</td>
<td>2.23 *</td>
</tr>
<tr>
<td>4-5</td>
<td>38</td>
<td>5.18 *</td>
<td>2.38 *</td>
</tr>
</tbody>
</table>

Boyd 2005
## Risk of Surgical Complications by Frailty

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Intermediately frail patients, odds ratio (95% CI)</th>
<th>Frail patients, odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation category*</td>
<td>2.02 (1.22–3.34)</td>
<td>3.12 (1.48–6.57)</td>
</tr>
<tr>
<td>Operation category and ASA score</td>
<td>2.13 (1.27–3.59)</td>
<td>3.15 (1.47–6.72)</td>
</tr>
<tr>
<td>Operation category and Lee score†</td>
<td>1.99 (1.19–3.33)</td>
<td>2.68 (1.23–5.87)</td>
</tr>
<tr>
<td>Operation Category and Eagle score†</td>
<td>1.78 (1.06–3.02)</td>
<td>2.72 (1.25–5.90)</td>
</tr>
<tr>
<td>Adjusted for all factors (parsimonious model)</td>
<td>1.97 (1.16–3.35)</td>
<td>2.48 (1.11–5.56)</td>
</tr>
<tr>
<td>Adjusted for all factors (forced model)</td>
<td>2.06 (1.18–3.60)</td>
<td>2.54 (1.12–5.77)</td>
</tr>
</tbody>
</table>

*Operation category includes operation types, major versus minor, intra-abdominal versus extra-abdominal, and open operation versus percutaneous or minimally invasive procedure.

†Lee and Eagle are cardiac preoperative risk stratification systems.

ASA, American Society of Anesthesiologists.

Makary et al, 2010
Figure 1. (A) American Society of Anesthesiologists (ASA), (B) Lee, and (C) Eagle risk indices. Each panel shows the area under the receiver operator characteristics (ROC) curve to demonstrate the ability of the specific risk index to predict surgical complications and discharge to an assisted or skilled nursing facility. Frailty was added to the risk index scoring to demonstrate the combined ability of these indices to predict discharge disposition.
### Increased Length of Hospital Stay by Frailty

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Intermediately frail patients, IRR (95% CI)</th>
<th>Frail patients, IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation category*</td>
<td>1.53 (1.28–1.83)</td>
<td>1.89 (1.43–2.48)</td>
</tr>
<tr>
<td>Operation category and ASA score</td>
<td>1.50 (1.25–1.79)</td>
<td>1.80 (1.36–2.37)</td>
</tr>
<tr>
<td>Operation category and Lee score</td>
<td>1.51 (1.26–1.80)</td>
<td>1.74 (1.32–2.30)</td>
</tr>
<tr>
<td>Operation category and Eagle score</td>
<td>1.44 (1.2–1.73)</td>
<td>1.65 (1.25–2.18)</td>
</tr>
<tr>
<td>Adjusted for all factors (parsimonious model)</td>
<td>1.49 (1.24–1.80)</td>
<td>1.67 (1.27–2.21)</td>
</tr>
<tr>
<td>Adjusted for all factors (forced model)</td>
<td>1.49 (1.24–1.80)</td>
<td>1.69 (1.28–2.23)</td>
</tr>
</tbody>
</table>

*See Table 2.

ASA, American Society of Anesthesiologists; IRR, incidence rate ratio.

Makary et al, 2010
Prognostication based on frailty status

- Courses of death
  - 20%: fatal illness: a few weeks to months of rapid decline prior to death; median: age 65
  - 25%: slow decline in physical capacities punctuated by serious exacerbations; eg., CHF, COPD; median age 75
  - 40%: longterm dwindling of function, with years of personal care; eg., frailty, cognitive impairment; dying occurs after physiological challenge; median age 85
Model of Typical Illness Trajectory for Dementia or Frailty

J. Lynn and DM Adamson. Rand Health 2003
Exhaustion

Under-nutrition

Weight Loss

Strength

Exhaustion

Physical Activity

Walking Speed

Xue, Fried et al
Many modifiers of frailty with aging

- Acute stressors; immobilization
- Catabolic/inflammatory diseases
- Medications
- Physical activity
- Dietary intake;
  - Taste and smell; anorexia of aging or disease
  - Access to food, due to disability, neighborhood, poverty
  - Social isolation, depression
CHS: Ankle-arm index <0.9 (prevalence, adjusted for age, gender, and race) by frailty status in those with and without prevalent clinical cardiovascular disease and total

One model for such a Win-Win: Experience Corps

- High intensity volunteering for older adults
- High impact roles in public elementary schools improving outcomes for children
- Critical mass of older adults:
  - Shift outcomes for schools
  - Force for social benefit
  - Social networks and friendships
- Health promotion program embedded
  » Fried et al, 2004
  » Rebok et al, 2011
Social Health Promotion: Experience Corps Model

- Volunteers 60 and older
- Serve in public elementary schools: K-3
- Meaningful roles; important needs
- High intensity: ≥15 hours per wk
- Reimbursement for expenses: $250/mo
- Sustained dose: full school year
- Critical mass, teams
Experience Corps: Potential Model of the Win-Wins of an Aging Society

• **Societal benefits of an aging population:**
  – Improve academic success of children in schools through the roles of older adults
  – In young countries, secure successful transition of youth bulge, second demographic dividend

• **Societal approach to addressing needs of older adults:**
  – *Roles that meet generative desires*
  – *Enhancing healthy aging? Prevent or slow disability, frailty, falls, memory impairment*
“IT SEEMED A GOOD OPPORTUNITY TO HELP OUT.”

DICK FRYER, 73, HAS A PRIVATE CHAT WITH A SECOND-GRADE OUTSIDE THE CLASSROOM. A RETIRED CIVIL ENGINEER FROM PERRY HALL, FRYER LEARNED ABOUT THE EXPERIENCE CORPS THROUGH AN AARP MAILING.
Evidence-based, Standardized Roles for Older Volunteers

- *Experience Corps, U.S.* -

- **Academic support:**
  - Literacy support
  - Opening/maintaining school libraries
  - Math support
  - Computer support

- **Behavioral support:**
  - Conflict resolution, positive attention

- **School attendance**
- **Parental outreach**
- **Public Health: Asthma club**
- **More roles to come**
Causal Pathway: Experience Corps

Intervention

- Experience Corps Participation - Generative Role Performance

Primary Pathways

- Physical Activity
- Cognitive Activity
- Social Activity, Engagement

Mechanisms

- Cortical plasticity; Memory Executive function
- Social Integration & Support Generativity
- Strength, balance

Performance-based measures
- Secondary outcomes and intermediate mechanisms
  - Falls
  - Walking Speed
  - Frailty
  - Complex task performance
  - IADLs
  - Psycho-Social Well-being

Primary/ [Self Report] Outcomes

↑ or preserved function or delayed decline in:

- Social Integration & Support
- Engmt.
- Generativity
- Physical Activity
- Cognitive Activity
- Social Activity, Engagement

Causal Pathway: Experience Corps

Mobility Function
EC Pilot Trial: Changes in Activity Pathways:
Increased walking & decreased sedentary activity

Fried et al., 2004
Program Components Targeting Multiple Cognitive Abilities and Associated Brain Substrates

• Embraces environmental complexity:
  – Broad vs. specific intervention design
  – Embedded within everyday activity
  – Novelty: Every day is different

• Multiple roles (e.g., tutoring, library & math):
  – Flexibly shifting across roles & group vs. 1 on 1
  – Variety; stimulating multiple domains of ability

• Problem solving with team members & teachers

• Designed to generalize to multiple cognitive abilities
Do Improvements Get Under the Scalp?
Intervention-specific Improvements in those With Poor Baseline Executive Function at Baseline; EC pilot RCT

Carlson, Saczynski, Rebok, et al., 2008
Pilot Evidence:

EC Improved executive function and increased activation in prefrontal cortex

Carlson, Erickson, Kramer, Colcombe, Bolea, Mielke, Rebok & Fried, 2009
Preliminary Conclusions: fMRI pilot trial

• Brain plasticity evident from EC high intensity roles; these involve learning, adaptation, mental flexibility

• Change in patterns of brain activation in areas consistent with executive function changes

• EC-related improved ability to selectively attend during most demanding conditions.
Implications of EC for older adult volunteers

• Generativity: Critical mass with high retention – affects whole grades of children;

• Sustained dose of health promotion/prevention: modification of key risk factors for healthy aging
“YOU ARE A FRIEND IN THE CLASSROOM.”

AUDREY WEEMS, 70, READING A STORY TO STUDENTS IN A THIRD-GRADE CLASS AT WAVERLY. A MOTHER OF EIGHT, SHE WORKED AT THE SOCIAL SECURITY ADMINISTRATION FOR 35 YEARS, RETIRING IN 2002. WEEMS LEARNED ABOUT THE BALTIMORE EXPERIENCE CORPS PROGRAM THROUGH HER CHURCH.
Broad Implications: We can create “both-and” bigenerational benefits through one investment

- Evidence-based designs bring impact
- Cross-generational legacy
- Health and wellbeing: current and future older adults
- Health disparities
- Win-Win of an aging society
In vivo nuclear MRS experiments re: energetic abnormalities in skeletal muscle in IL10 frail mice:

Skeletal muscle concentrations of ATP, Phosphocreatine (PCr) and inorganic phosphate (Pi)

Akki A et al, Age, 2013
Skeletal Muscle Energetics:

CK pseudofirst order rate constant ($k_{\text{PCr} \rightarrow \text{ATP}}$) and rate of ATP synthesis through CK

Akki A et al, Age, 2013