

Frailty and Aging: The last 10 years of aging research, and next steps

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The evolution of understanding frailty as a geriatric syndrome:

1980's: frailty = old old age; multimorbidity; disability

1990's: differentiating aging from disease, multimorbidity and disability, and began differentiating frailty.

2000's: frailty as a distinct geriatric syndrome, vulnerable state, distinct pathophysiology

2009 and beyond:

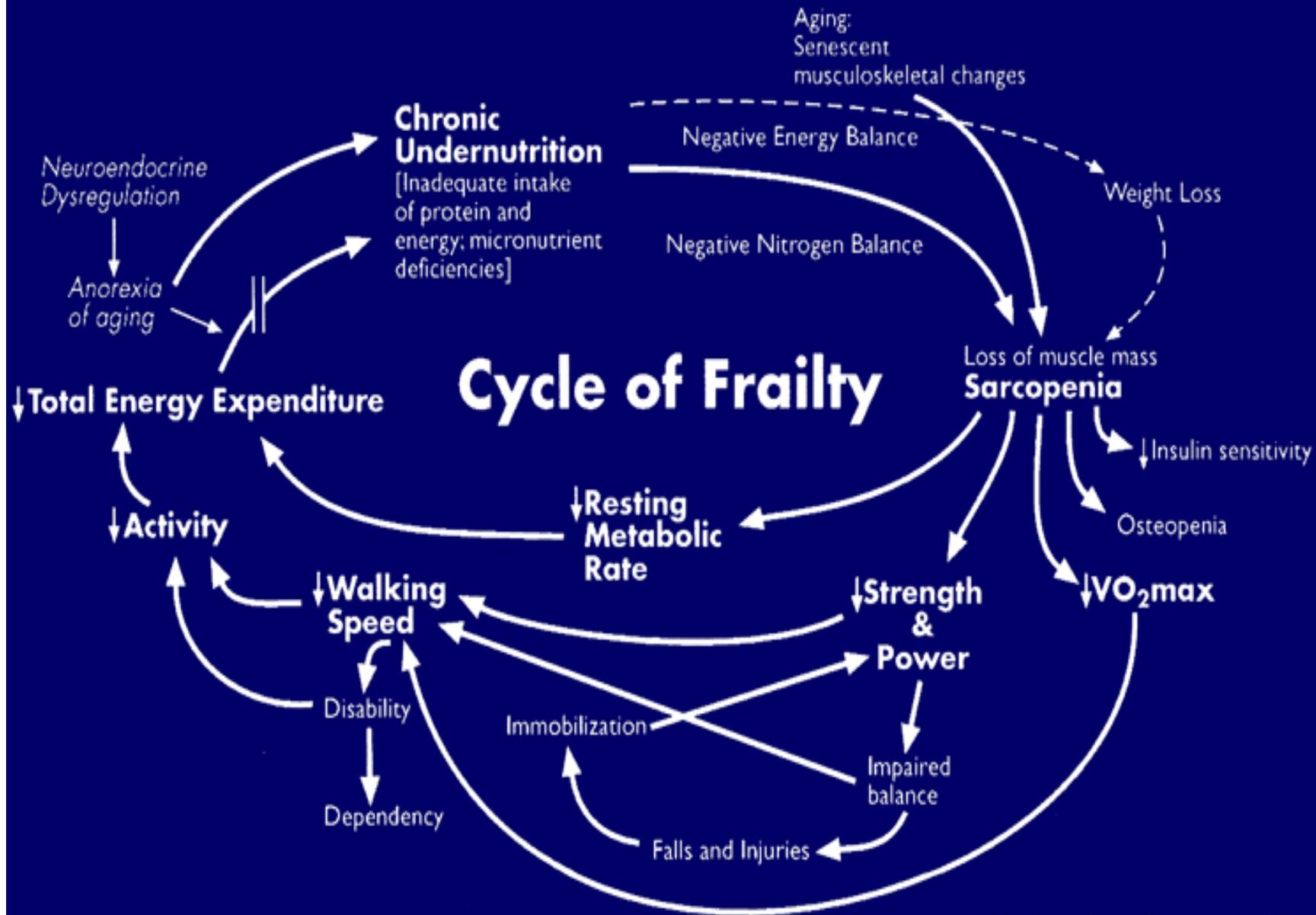
- Frailty syndrome = emergent property of dysregulated complex system; energetics etiology
- Frailty syndrome = 1/resilience;
- Accumulated damage may be one pathway that triggers the endpoint of frailty syndrome.

2015 and beyond: the new geroscience: seeking shared pathways to frailty, aging and disease.

Commonly Identified Features of Physical Frailty – among Geriatricians 1990's

- Declines in lean body mass, strength
- Weight loss
- Loss of endurance
- Slowed walking performance
- Relative inactivity
- Decreased balance and mobility

Why do these co-occur on the same list?



(Fried and Walston, 1998)

Phenotype of Frailty, as operationalized in CHS

<u>Characteristic</u>	<u>CHS Study Measure</u>
Shrinking	Unintentional weight loss >10 lbs, past year; F/U: $\geq 5\%$ weight loss over 1 year
Weakness	Grip strength: lowest 20%
Slowness	Walking time: lowest 20%
Poor endurance	Exhaustion (self report)
Low activity	Kcal/week : lowest 20%

Non-frail: 0/5

Pre-frail: 1 or 2/5

Frail: 3, 4, or 5/5

(Fried LP et al, JGMS 2001)

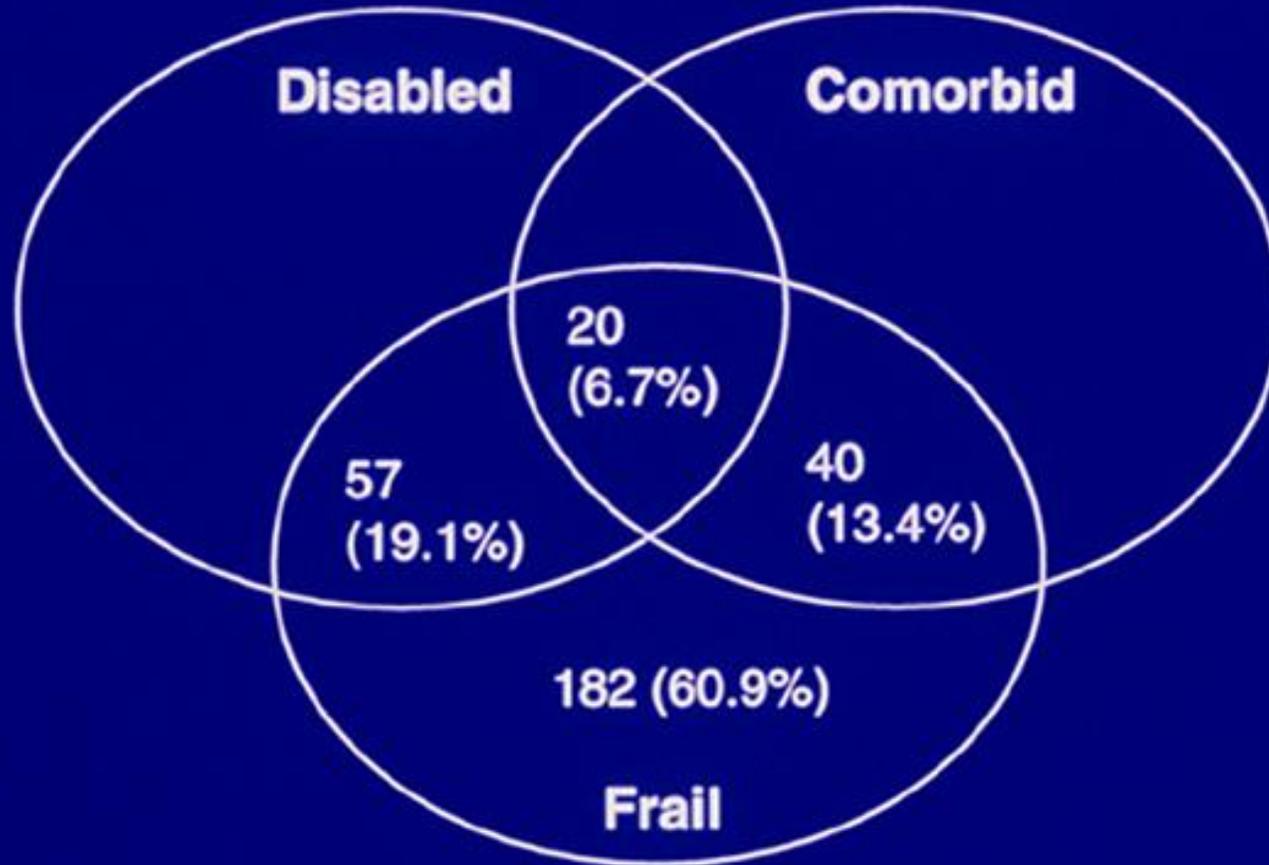
A distinct frailty phenotype is prevalent: 2015

>65, community dwelling, US:

- 15% are frail;
 - prevalence increases geometrically with age, from 9% 65-69 to 38% 90+
- 45% prefrail

(Bandeem Roche et al, J Gerontol Med Sci 2015; NHATS)

Frailty, Disability and Comorbidity in CHS



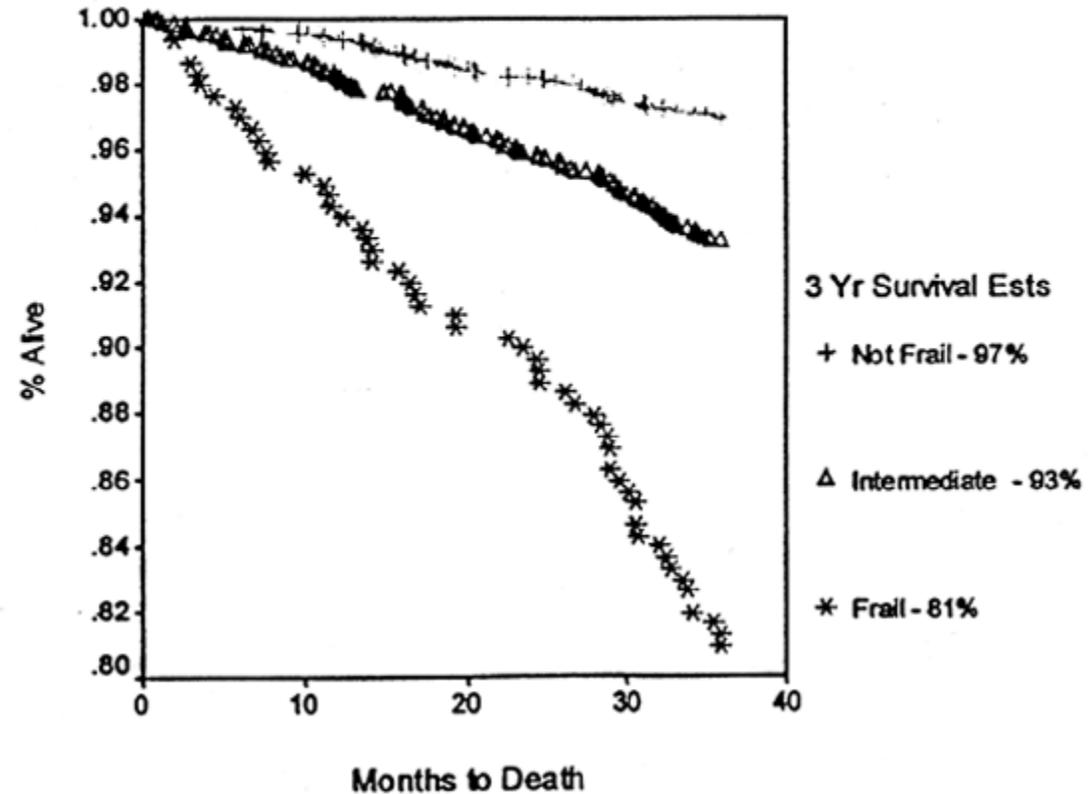
Fried 2001

Frailty phenotype validated in U.S. community-dwelling cohorts

- *Cardiovascular Health Study*
 - men and women 65-101 years at baseline
- *Women's Health and Aging Studies I & II (WHAS)* combined:
 - Women 70-79 years, drawn from:
 - 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)

Unadjusted 3 Year Survival Estimates by Frailty Category



Fried 2001

Risk: ≥ 3 criteria present predict
high risk of adverse outcomes

(Significantly more than any 1 or 2 criteria; **independent of Diseases**)

- **Mortality, disability, falls, hospitalization, surgery, burns, slow recovery –**

(Fried 2001)

Predictors of 5 year mortality in older adults - *Cardiovascular Health Study* -

20 characteristics (of 78 assessed) significantly, independently and jointly predict mortality:

- Demographics: Age (over 85), male
- Lifestyle: physical activity, smoking, elevated SBP, fasting glucose
- Clinical disease: CHF
- Physical function: difficulty with 2 or more IADLs; not walking speed
- *Objective noninvasive measures: major ECG abnormality, abnormal LVEF and Aortic stenosis (echo); max stenosis of internal carotid artery (ultrasound); FVC
- *Biochemical measures of disease: creatinine, albumin;
- *Cognitive function: DSS

(Fried LP et al; JAMA 1998)

Frailty phenotype is consistent with definition of a *clinical syndrome*

The whole is greater than the sum of the parts:

1. Aggregate phenotype predicted mobility disability and other outcomes better than individual markers – eg, walking speed, strength, weight loss, physical activity, exhaustion
2. No tendency for distinct subsets of items to aggregate in different classes
3. Rather, stepwise progression in prevalence of each criterion across classes, consistent with overall aggregation (Bandeem-Roche K, et al, J Ger Med Sci 2005)

- Follow-on studies: phenotype identifies **specific pathophysiologic biomarkers and potential processes**
- **Cross-validation** in multiple studies

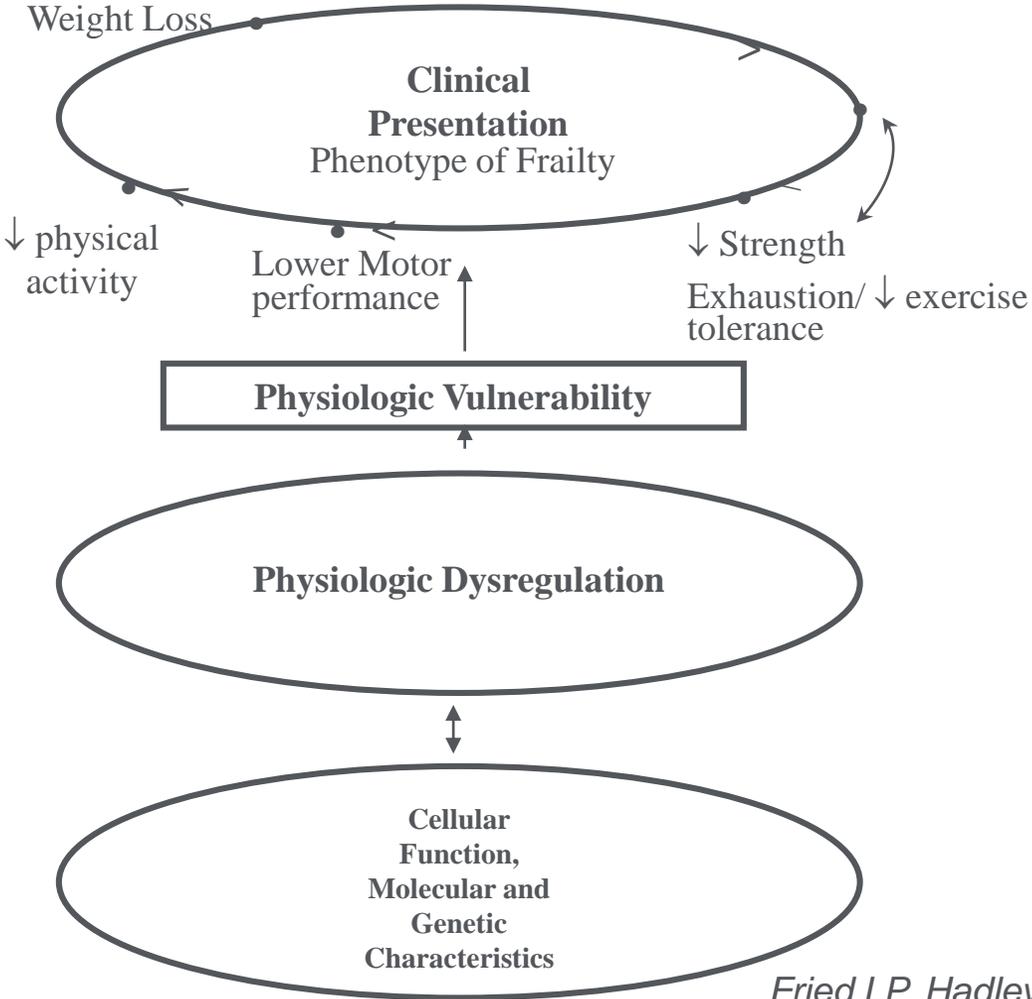
Frailty phenotype: Aggregate results of studies, 1998-2008

- Clinically observable presentation
 - Not the same as multimorbidity, disability, or extreme old age
 - Increases with age; females>males; blacks>whites
- Whole greater than sum of parts: behaves as a clinical syndrome
- Predicts disability and mortality independent of diseases; step wise increased risk in association with number of criteria present
- Inflammation and inflammatory diseases associated with frailty
- Natural history:
 - Those who are prefrail at high risk of becoming frail
 - Most severe phases: predeath, and not amenable to treatment

2009-2019: Frailty and aging

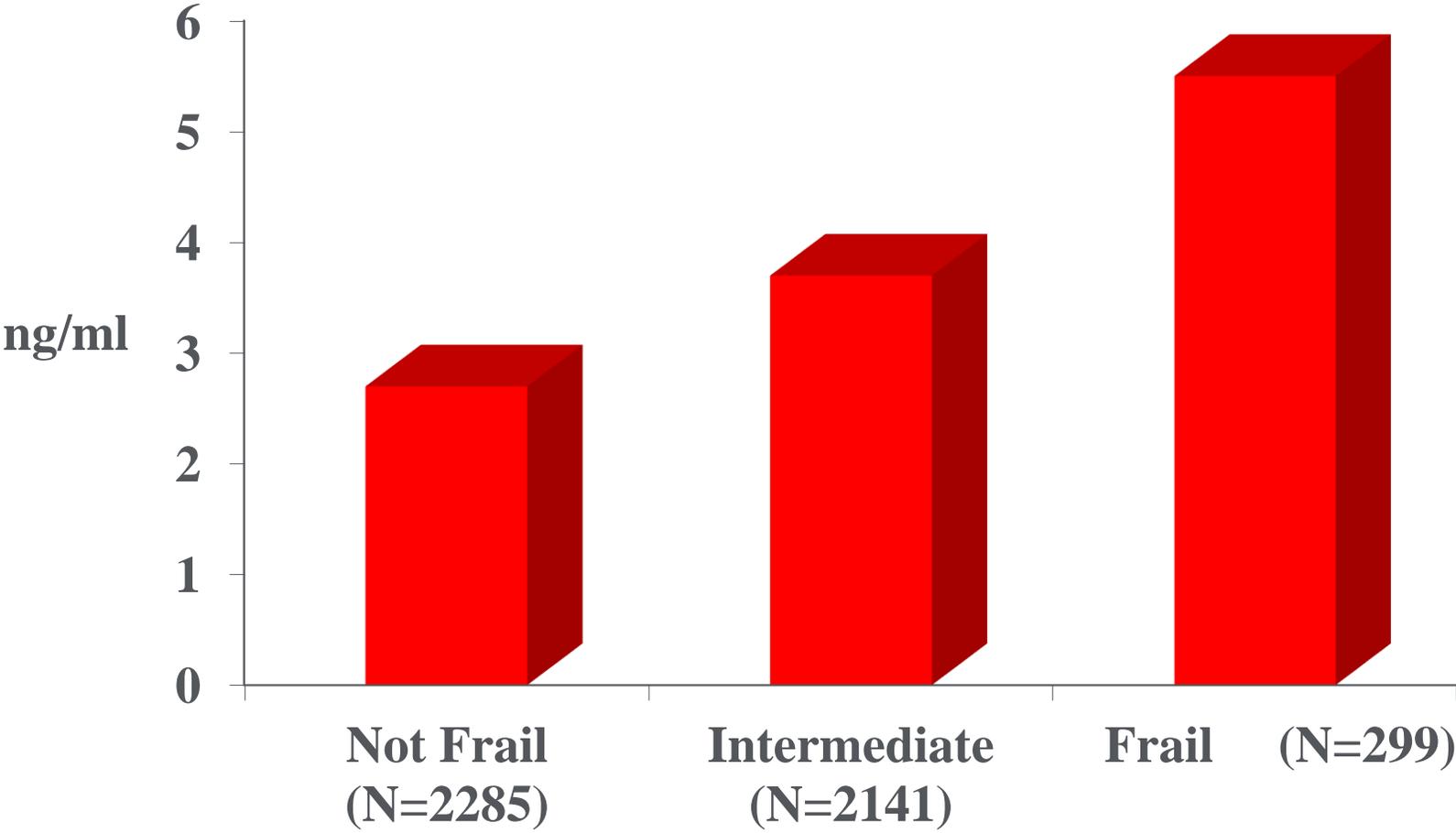
- *Probing the bottom of the iceberg*

Conceptual figure of syndrome of frailty



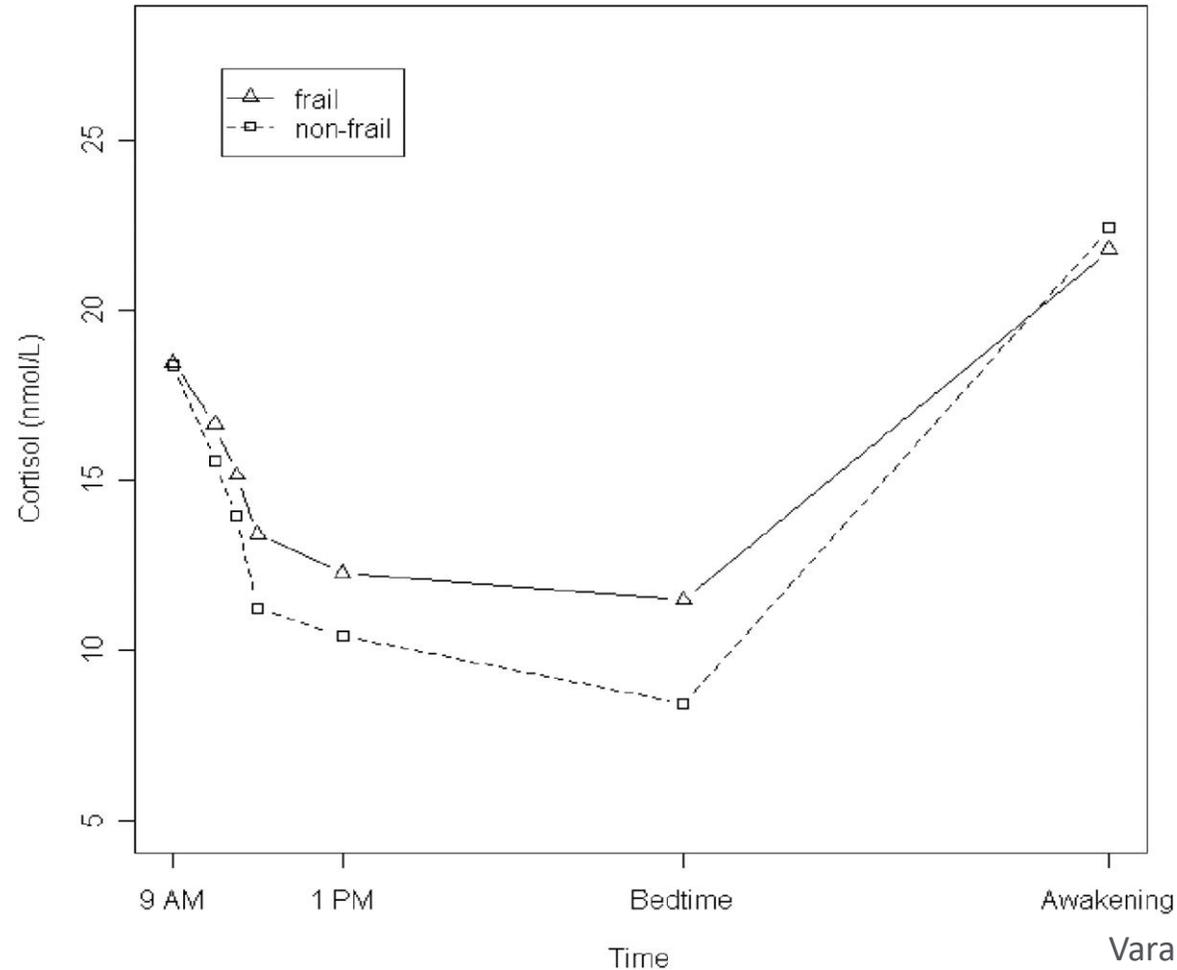
Fried LP, Hadley EC, Walston JD, et al. SAGE KE, 2005

Inflammation: C-Reactive Protein and Frailty, CHS



Walston, et al. Archives of Internal Medicine, 2002

HPA Axis: Mean diurnal salivary cortisol profiles over 24-hour period; WHAS II women 80-90 years



Varadhan et al, J Gerontol A Biol Sci Med Sci, 2008

Frailty phenotype associated with biomarkers of dysregulated physiologic systems: *window into potential pathological pathways*

- Sarcopenia
- Chronic low grade inflammation and immune activation, low platelets, anemia
- ANS: decreased heart rate variability
- Endocrine dysregulation
 - Carbohydrate metabolism: Glucose, insulin; elevated IR-HOMA, Hgb A1C $\geq 8\%$; metabolic syndrome
 - Energy metabolism: higher fasting leptin, resistin, GH; lower fasting ghrelin, adiponectin, GLP-1; u-shaped association with IGF-1
 - Adrenocorticoids/HPA: cortisol elevation
 - Low T, E, DHEAs

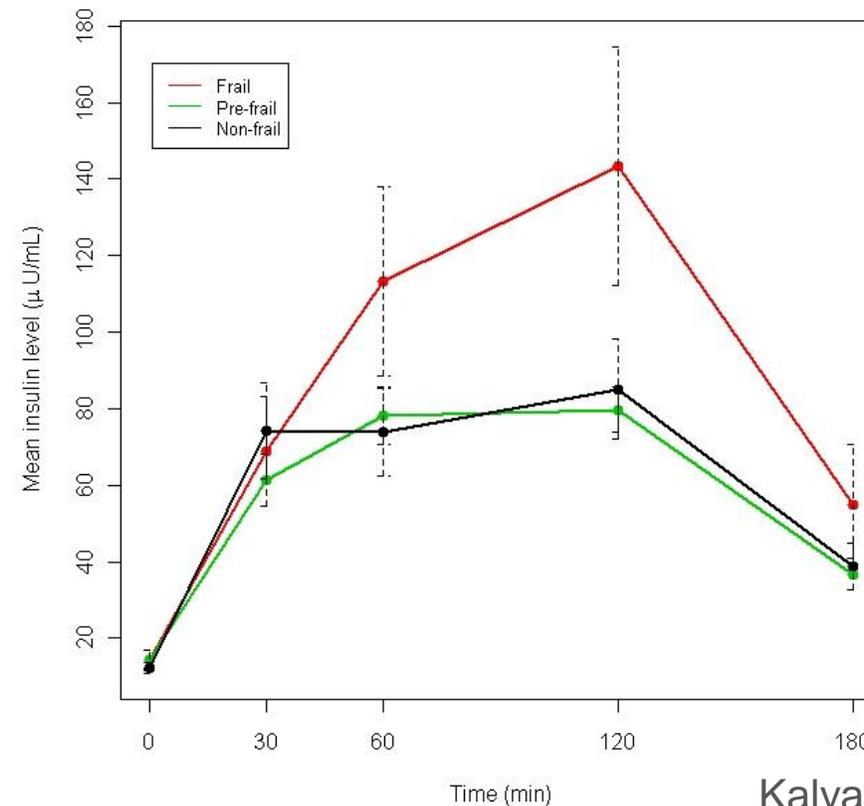
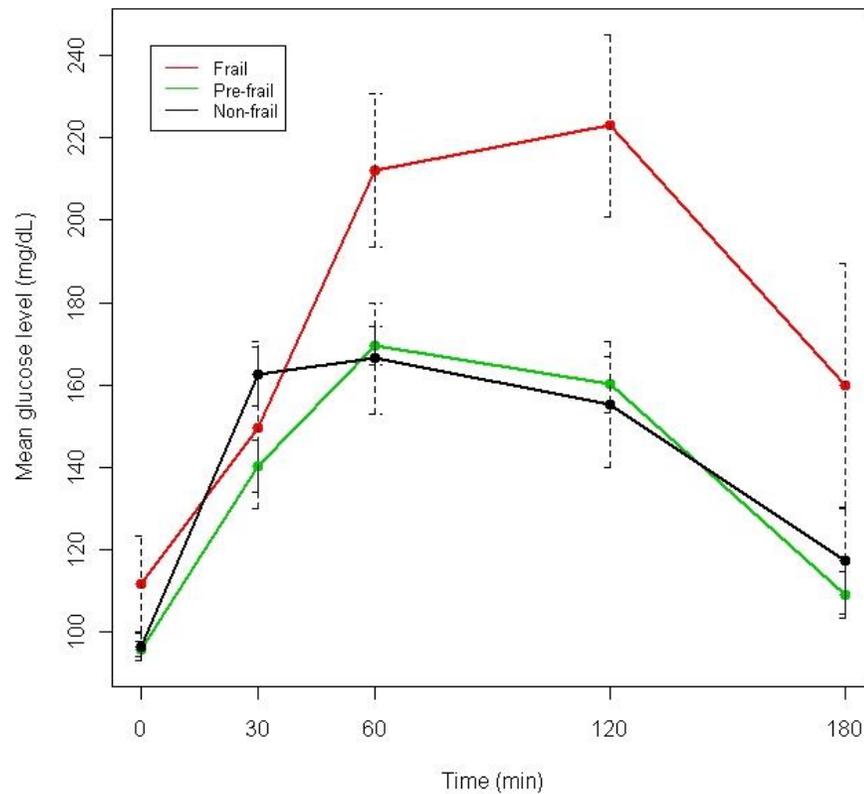
(Kalyani, 2011, 12; Walston 2002; Leng 2005; Cappola 2007; Varadhan 2010; Chaves 2009)

Biomarkers associated with frailty create a picture of multisystem dysregulation

- Many disease specific; also aging-related. Cause? Outcome?
- Are insulin resistance and inflammation shared aging-related pathways?
 - Underlying biology shaping biomarker dysregulation?
 - Shared pathways to disease and frailty?

How to understand vulnerability to stressors and high rates of adverse health outcomes associated with frailty?

Response to challenge: altered Glucose-Insulin Dynamics in Frail (vs. prefrail and nonfrail) in response to Glucose Tolerance Test (WHAS II, 73 nondiabetic women 84-93 years)



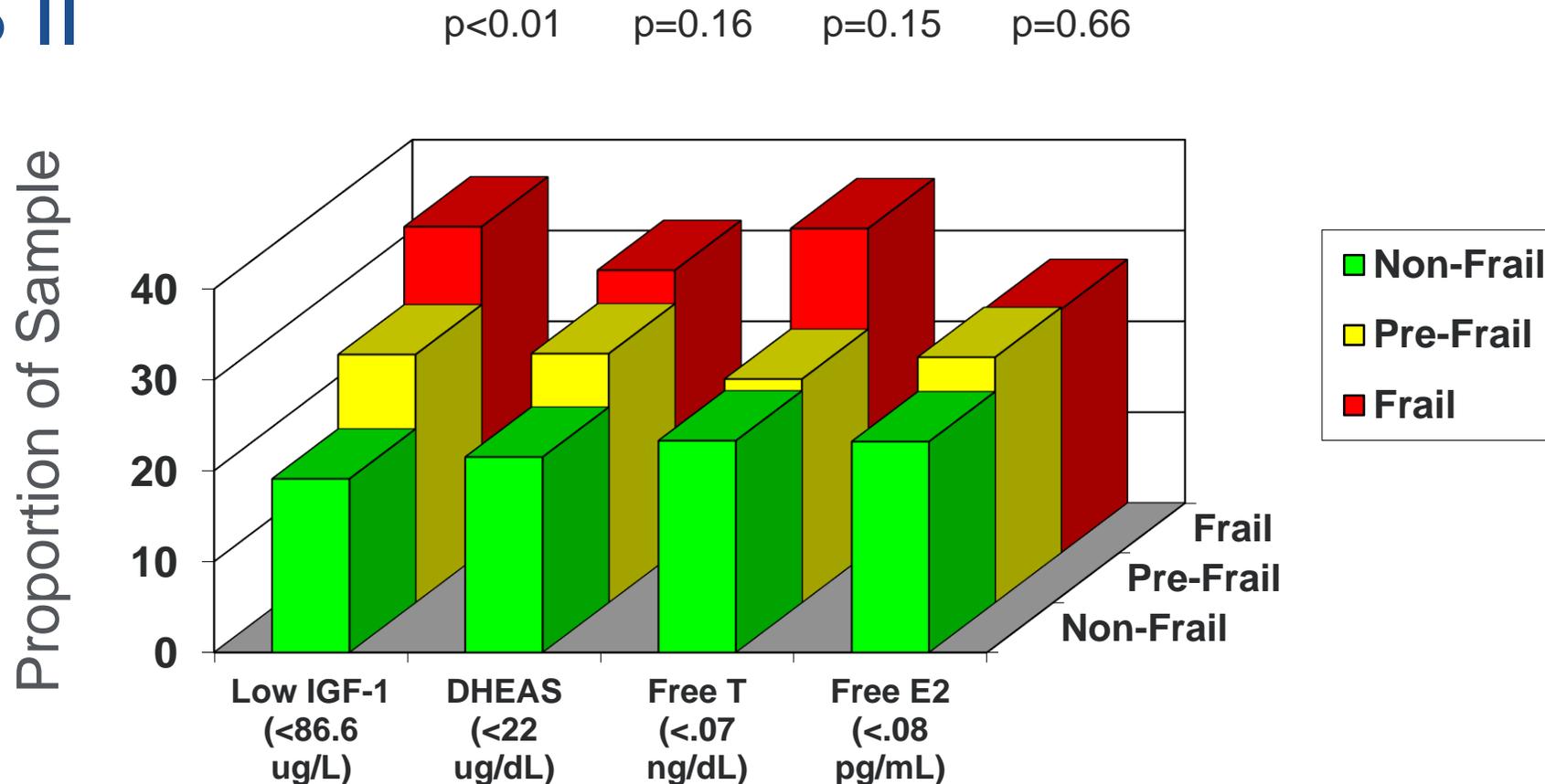
Kalyani et al. JGMS; 2011

Phosphocreatinine (PCr) recovery after 30- second isometric calf exercise, women 84-93

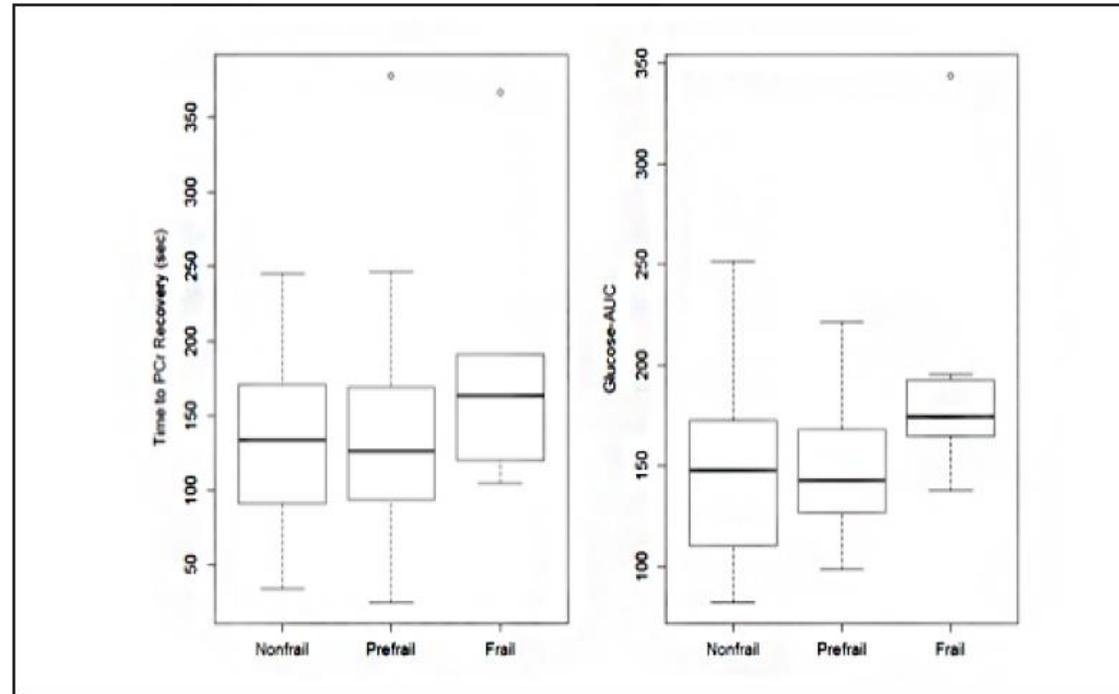
- Frail women had 43% slower PCr recovery, and prefrail 15% slower, than nonfrail; MRS.
- Implication: dysregulated energy production could contribute to the dysregulation of multiple physiologic systems associated with the frailty phenotype, as well as their mutual regulation of each other, and to diminished robustness required to maintain homeostasis under stress.

(Varadhan R, Russ DW, Gabr RE....Bandeem-Roche K, Fried LP. 2019. J Frailty Aging)

Prevalence of Frailty for 4 Hormone Deficiencies: crosssectional, WHAS II



Response to isometric exercise and GTT challenge tests, women 84-93, WHAS II



(Left panel) Time to 95% recovery of PCr after mild exercise;
(Right panel) area under the curve (AUC) of glucose levels over time after an initial glucose load in the glucose tolerance test

(Varadhan, Russ et al. 2018)

Implications re: energy homeostasis, dysregulation and frailty syndrome

- Phenotype: of dysregulated energetics
- Our stimulus-response challenge tests in women 83-95 years, frail v. prefrail v. nonfrail
 - *MR Spec: energy repletion slower; decreased mitochondrial function*
 - *Insulin resistance: utilization of energy inefficient or impaired*
 - *Ghrelin: less appetite stimulation; leptin resistant*

Post-challenge findings better differentiate physiologic status of frail v. prefrail and nonfrail

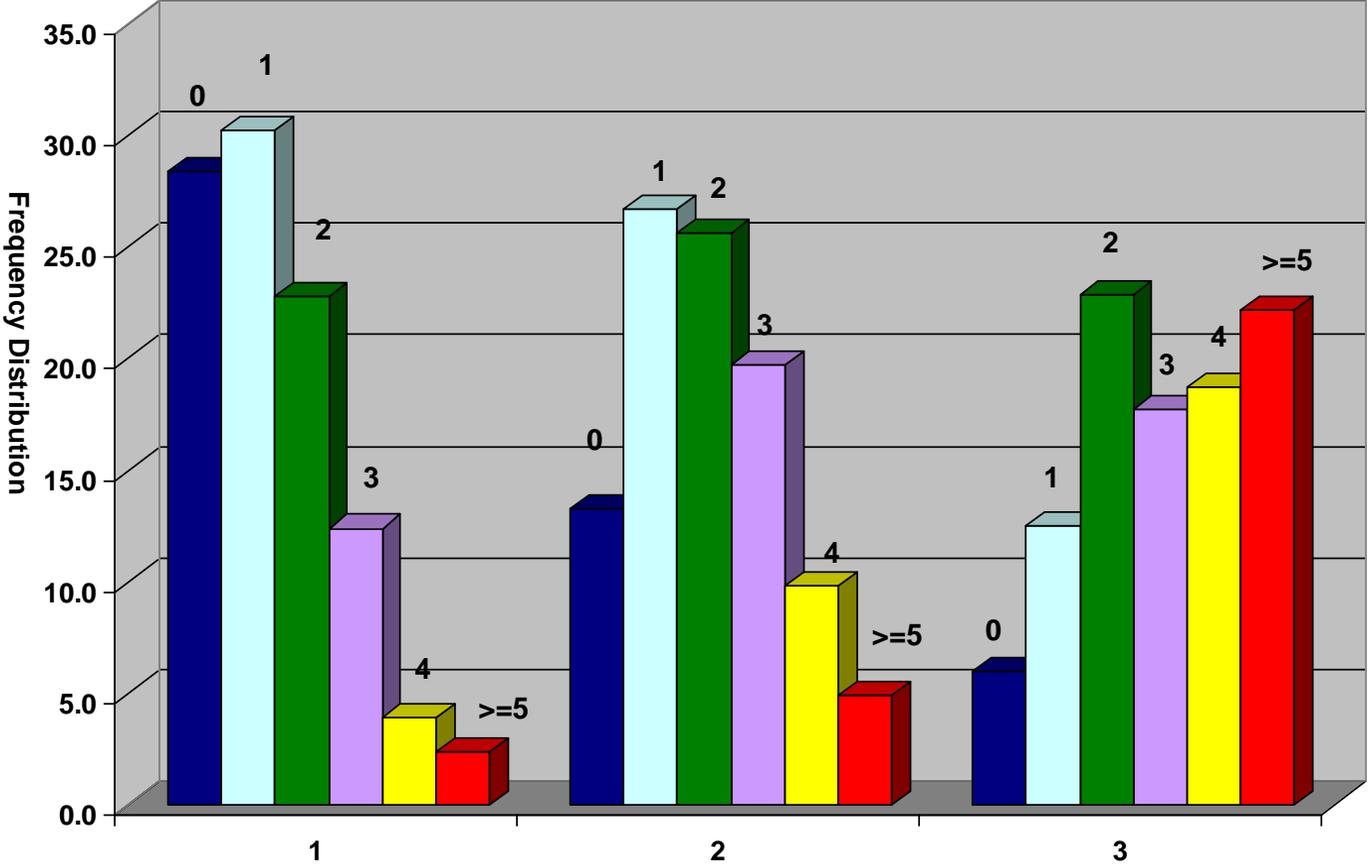
Implications:

- Biology of vulnerability
- Preclinical phase of frailty, perhaps along a continuum from resilient to frail
- Aligned findings in stress responses in multiple systems consistent with multisystem nature of frailty

Implications of multiple dysregulated systems associated with phenotype of frailty

Frailty emerges when multiple physiologic systems abnormal, out of 8 systems evaluated

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



Fried, Xue et al, 2008

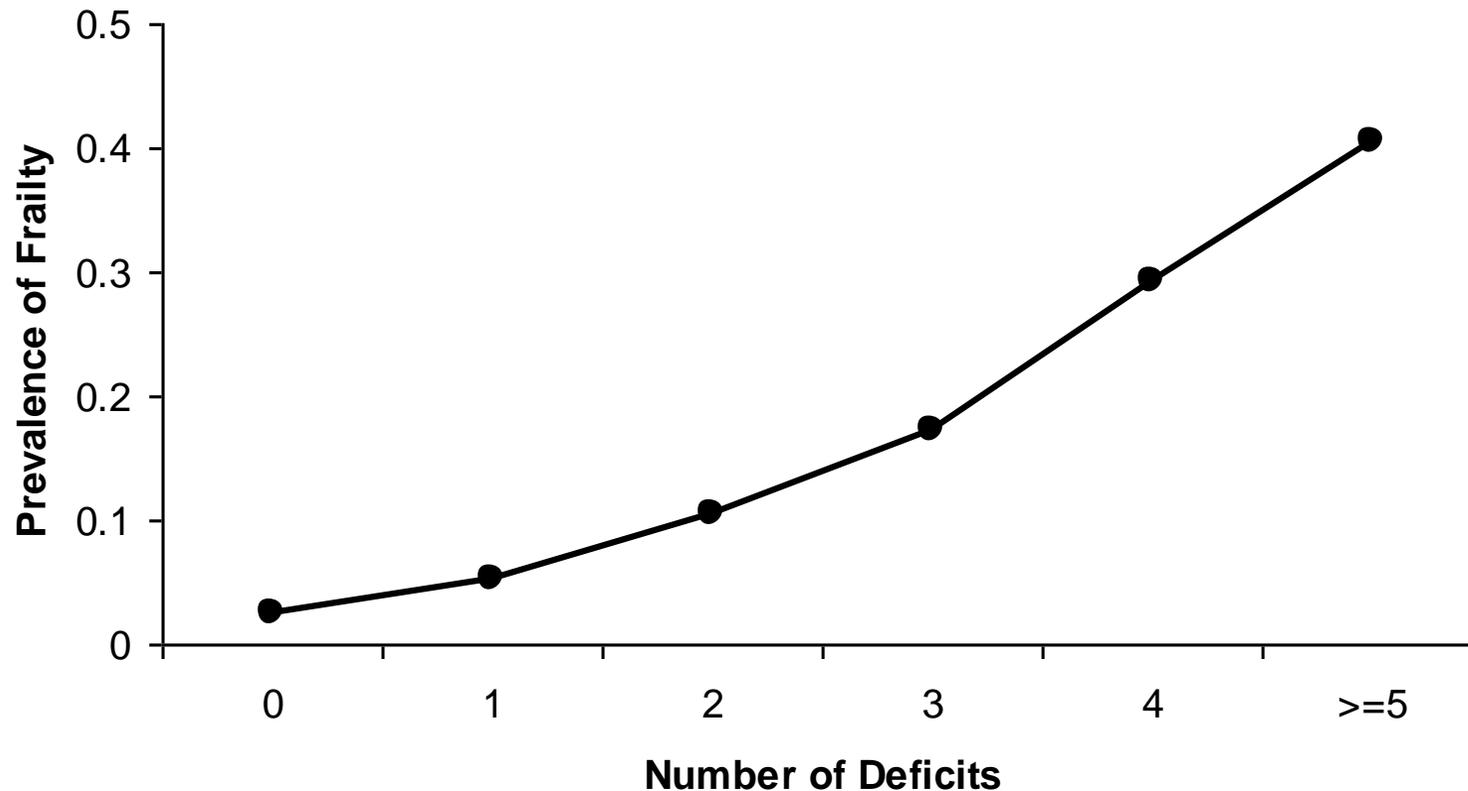
Associations of the Number of Physiologic Systems at Abnormal Levels with Frailty*, WHAS I/II

	Frail vs. Non-Frail
Number of Deficits	OR (95% C.I.)
0	1
1-2	4.8 [#]
3-4	11.0 ⁺
≥5	26.0 ⁺

* adjusting for age, race, education, and number of chronic diseases + p-value<0.01 ; # p-value < 0.05

(Fried et al 2009)

Evidence for Nonlinearity of Relationship of Number of Systems Abnormal with Frailty, WHAS I/II

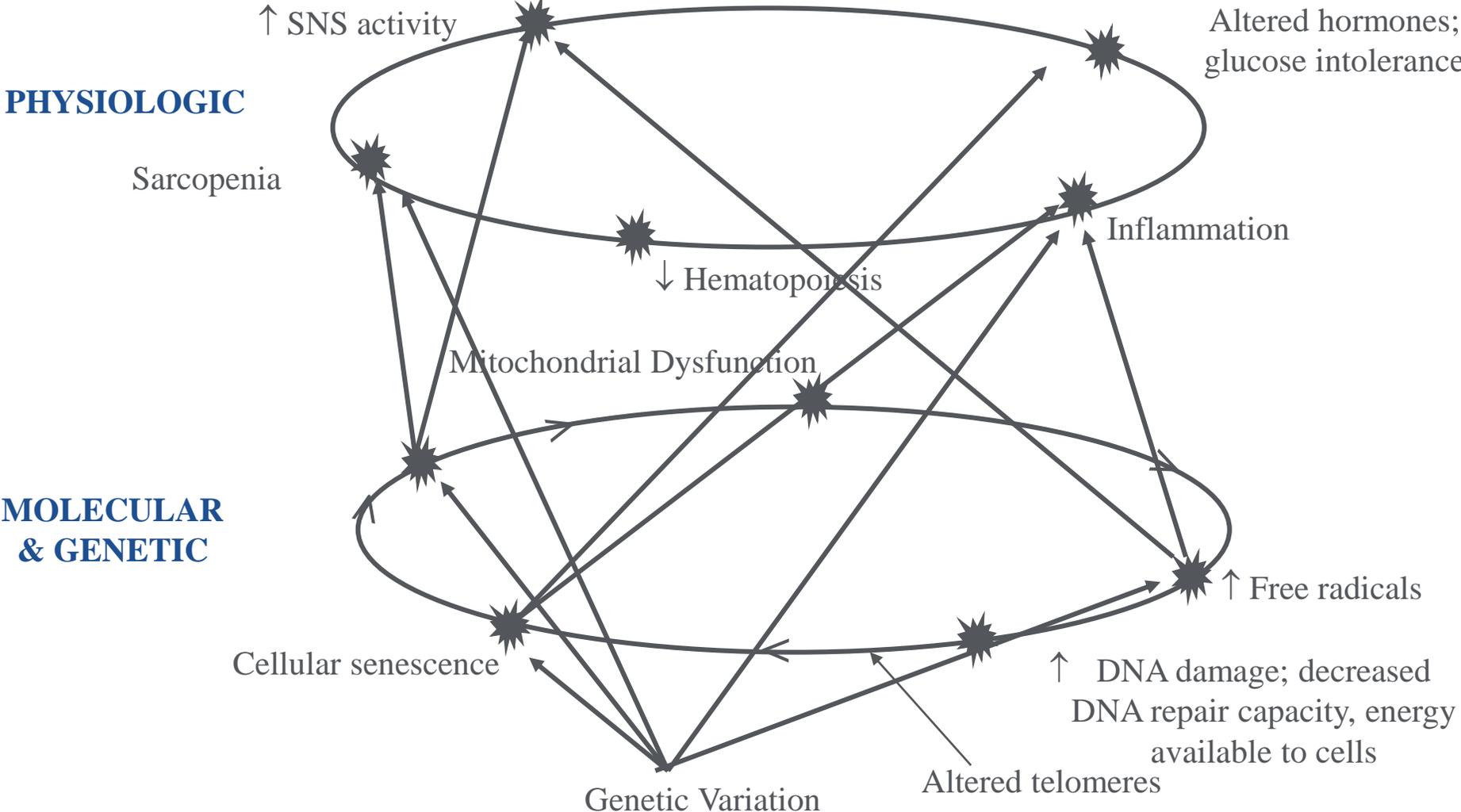


(Fried et al 2009)

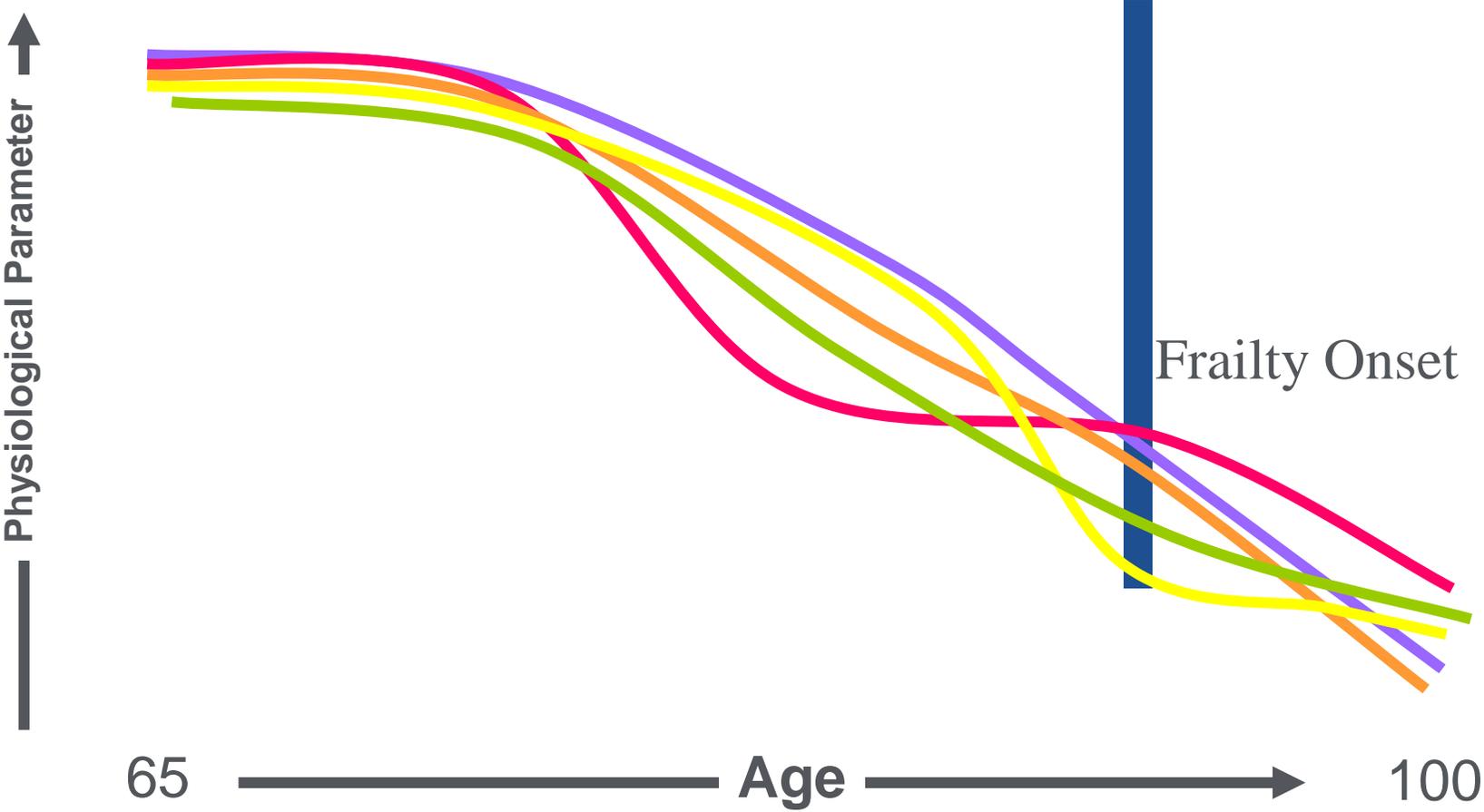
Nonlinearity: a characteristic of complex dynamical systems

- Nonlinearity: whole greater than sum of parts
- Mutual regulation of component modular systems; redundancy
- Emergent property: threshold of dysregulation below which organism functions at lower level
- Function at a suboptimal level may only be revealed under stress.
- Underpinning of robust and resilient organism
- Essential for maintenance of homeostasis
- Links physiology to clinical presentation

Multisystem Dysregulation and Interactions May Underlie Loss of Reserves, Frailty



Frailty: threshold dysregulation of integrated complex dynamical system



Is frailty syndrome a distinct process of accelerated aging?

Distinct from disease?

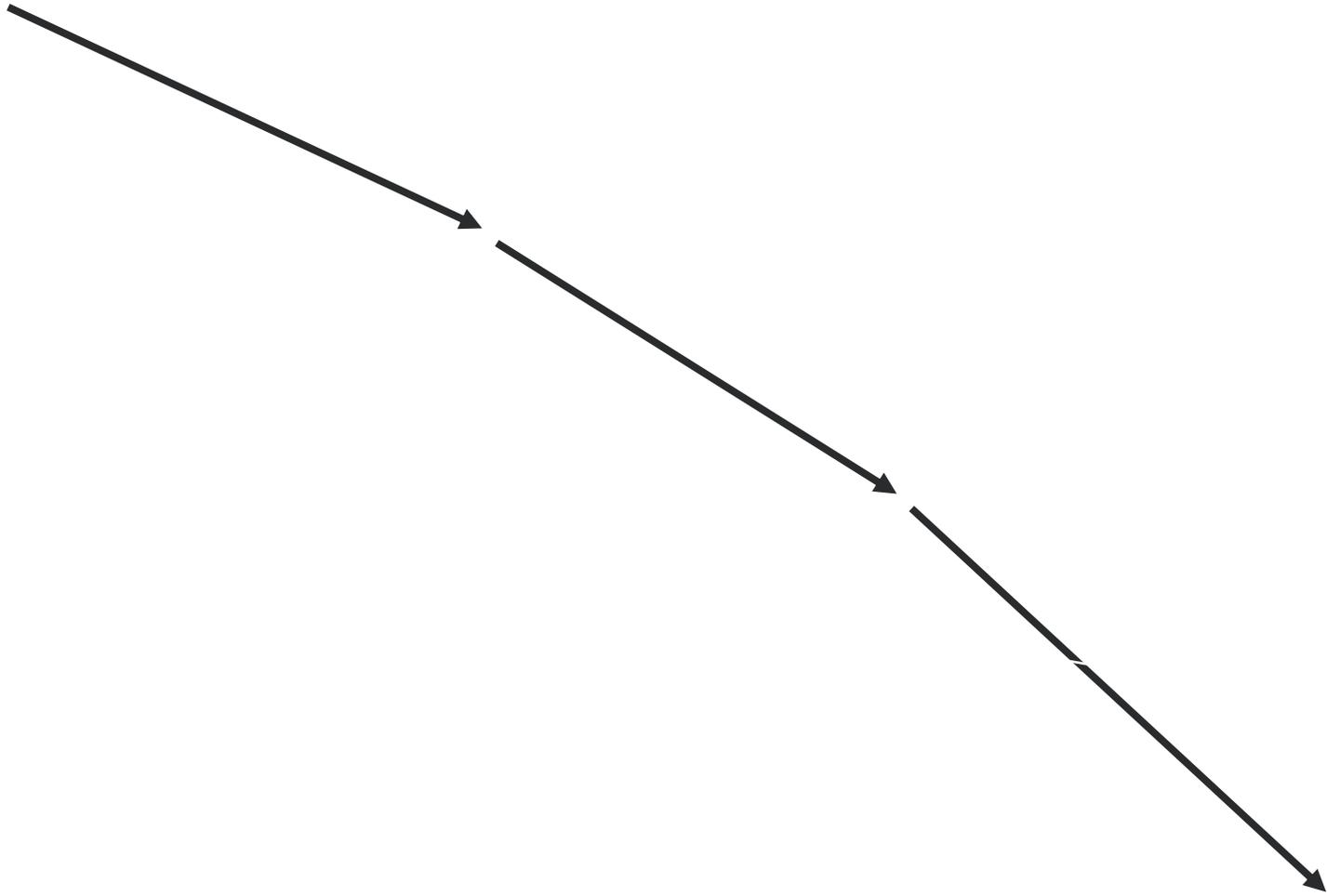
The inverse of resilience?

Shared etiologic factors?

Final common pathway of disease?

Interacting with disease?

Complex dynamical system:
Implications for treatment of only one
system in a complex system



Physical Activity: A model intervention for human frailty

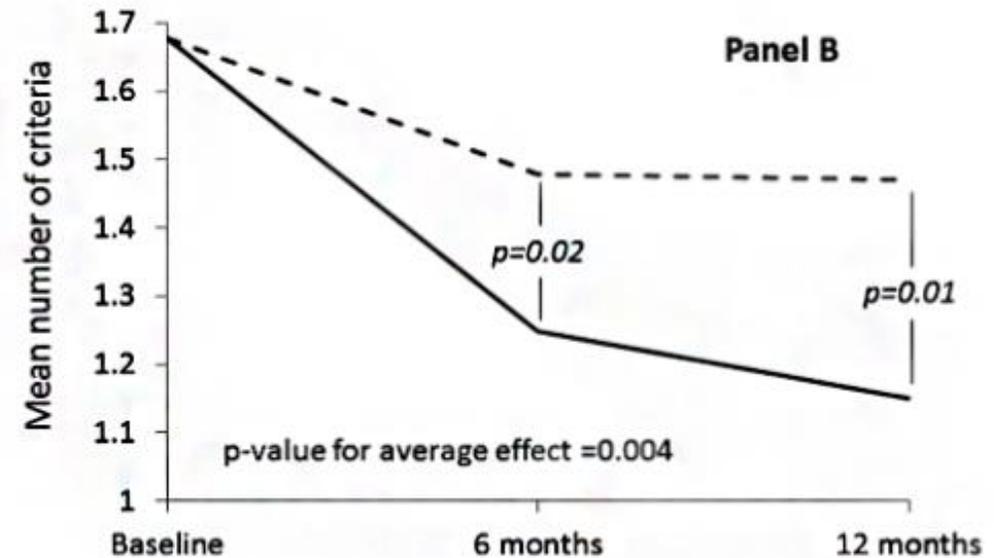
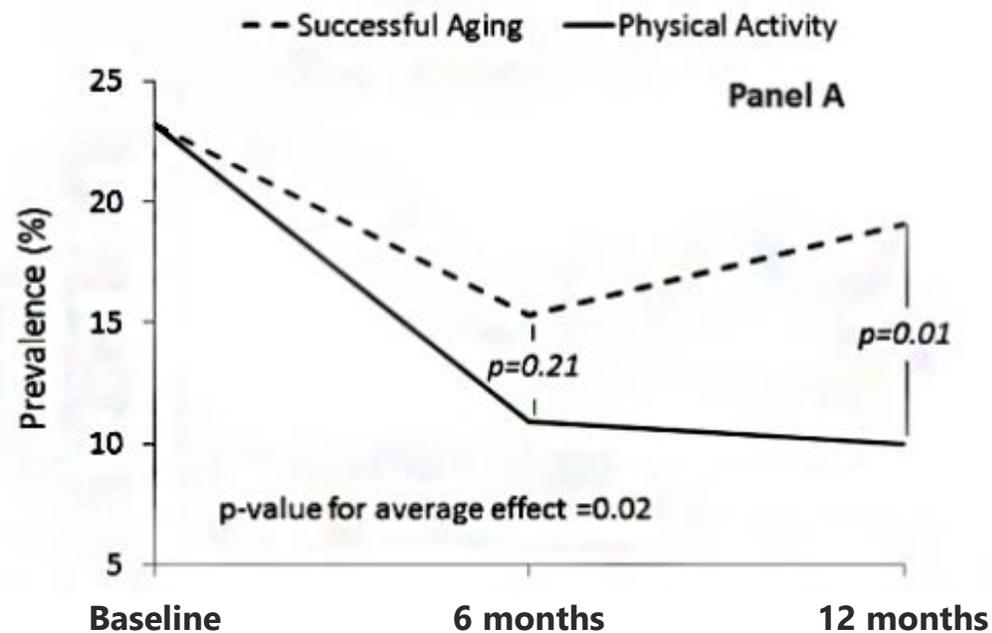
(Fried LP 2016, in Cold Spring Harb Perspect Med 2016; 6: a025916)

Physical Activity:
Tuning the energetics system that appears
dysregulated in frailty

Prevention of Frailty and Frailty Progression

Exercise associated with lower frailty incidence: LIFE RCT PA intervention pilot: GLM showing adjusted prevalence of frailty or number of frailty criteria

(N=424; age 70-89; 69% women, sedentary, high risk mobility disability)



(Cesari, Vellas et al 2015)

Ultimately, successful prevention of frailty involves intervening on both phenotype and the systems biology

Frailty, 2019: a window into the biology of vulnerability

- Reserves
- Homeostasis
- Resilience