RESEARCH CENTERS COLLABORATIVE NETWORK

RCCN Workshop

Measuring Biologic Age

January 19-20, 2022

VIRTUAL

Frailty / Physical Function underlying biology and potential treatment targets

Anne B. Newman, MD, MPH

Professor of Epidemiology and Medicine

University of Pittsburgh

Nothing to disclose

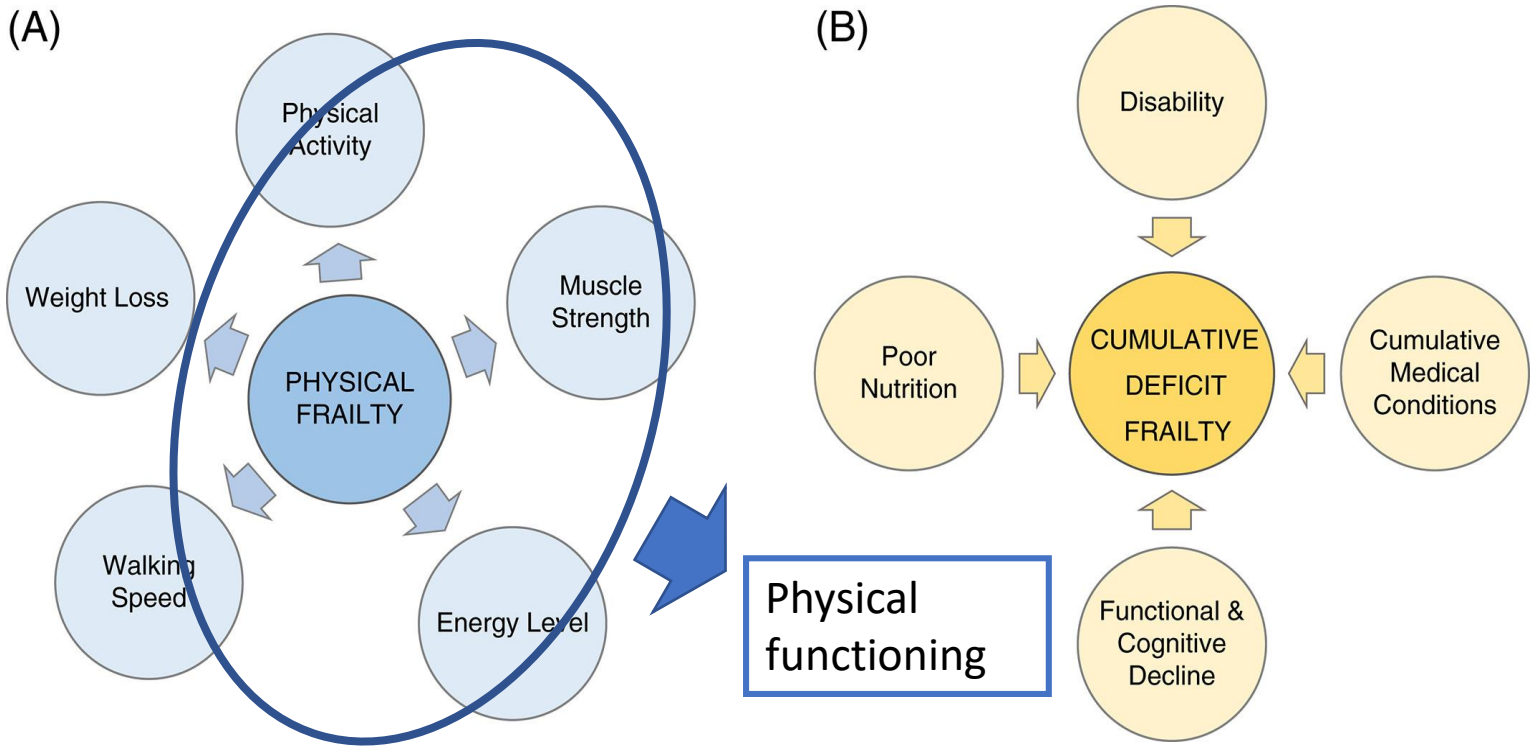
Frailty

- Deterioration in physiologic function
- Decline in ability to respond to stress
- Increase in vulnerability

Operational definitions of frailty

A) Frailty Phenotype

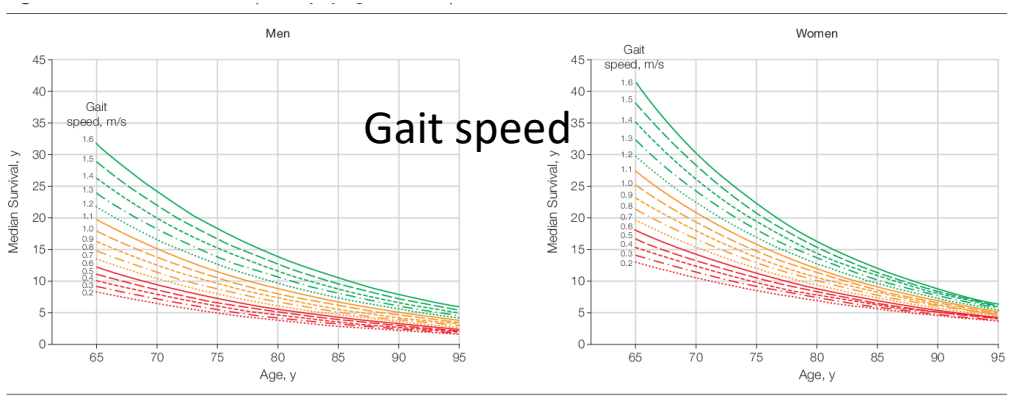
B) Frailty or Deficit Accumulation Index



Moving Frailty Toward Clinical Practice: NIA Intramural Frailty Science Symposium Summary

J American Geriatrics Society, Volume: 67, Issue: 8, Pages: 1559-1564, First published: 02 May 2019, DOI: (10.1111/jgs.15928)

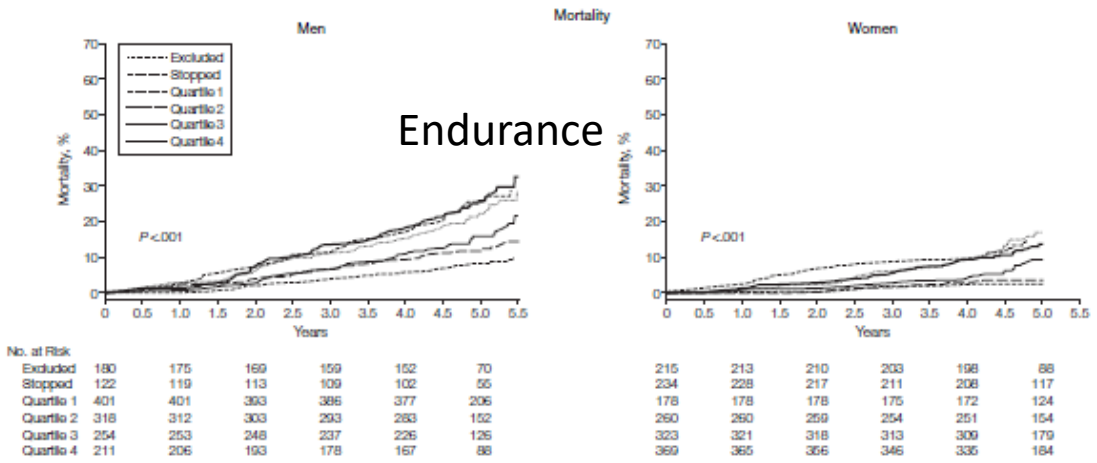
Physical function – Gait speed, strength, endurance



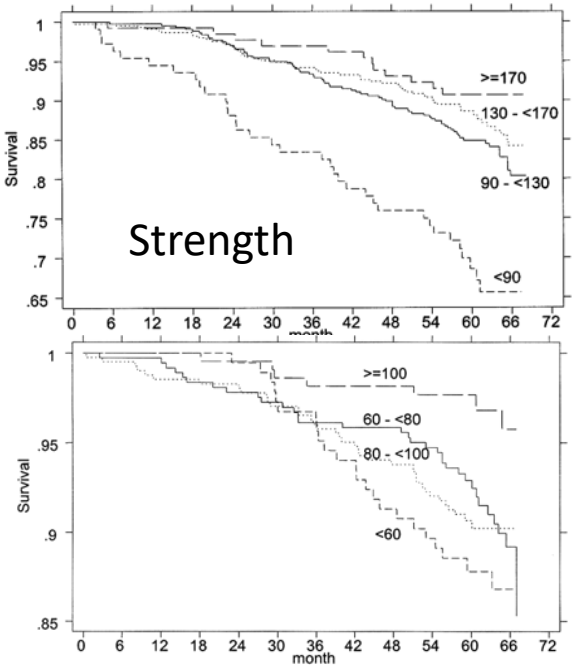
A PDF of enlarged graphs is available at http://www.jama.com.

Studenski, JAMA, 2011

Figure 2. Kaplan-Meier Plots of Mortality and Incident Cardiovascular Disease Event Rates



Newman AB, JAMA, 2006



Newman AB, JGMS 2006

Cognitive frailty

- Consensus definition- Reduced cognitive reserve evidenced by both physical and cognitive impairment (Kelaiditi E, Cesari M, JNHA, 2013, Buchman and Bennett, JNHA, 2013)
- Related - Motoric cognitive risk syndrome
  - Predicts dementia (Verghese, Alzheimer's & Dementia, 2019)
  - Predicts frailty (Sathyan, *Journal of Alzheimer's Disease,* 2019)
- Related - Dual tasking

Frailty and function as indicators of risk

- Frailty and poorer physical function robustly predict poor health outcomes
  - Mortality
  - Disability
  - Health Care Utilization
  - Tolerance of interventions
    - Surgery
    - Procedures
    - Chemotherapy

Physiologic systems important in physical function and frailty

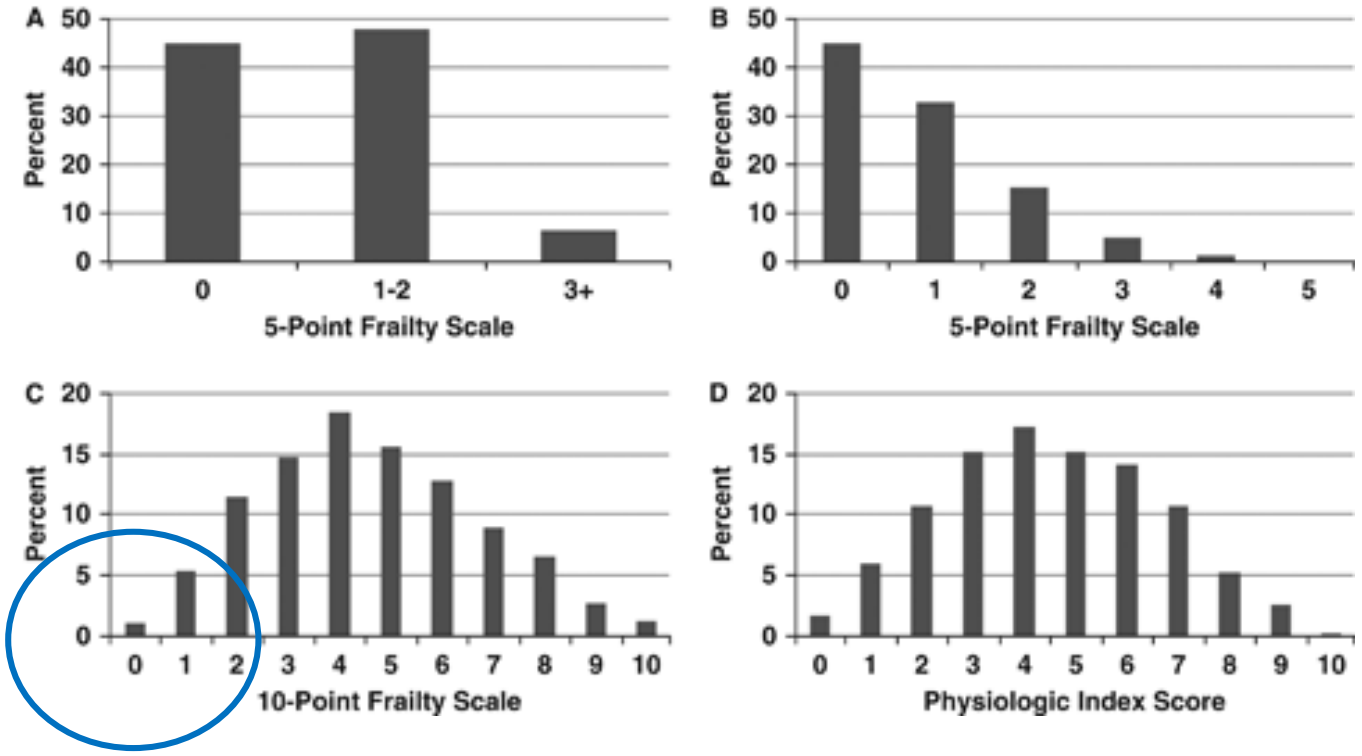
- Vascular system
  - Blood flow to brain and muscle
  - Endurance
- Neuromuscular system
  - Central control of movement, innervation of muscle
  - Strength and speed
- Sensorimotor system
  - Integration and feedback
- Metabolic system
  - Weight stability
  - Energetics of muscle and brain
- Immune system
  - Damage response
  - Chronic inflammation

Integration

Whole Person

Measurement of Organ Structure and Function Enhances Understanding of the Physiological Basis of Frailty: The Cardiovascular Health Study

Jason L. Sanders, MD, PhD



Similar distributions of frailty components as organ system components – carotid, brain WMG, lung function, kidney function, glucose tolerance

1 point of physiologic index = .3 points frailty

J American Geriatrics Society, Volume: 59, Issue: 9, Pages: 1581-1588, First published: 24 August 2011, DOI: (10.1111/j.1532-5415.2011.03557.x)

Do hallmarks of aging contribute to frailty and physical disability?

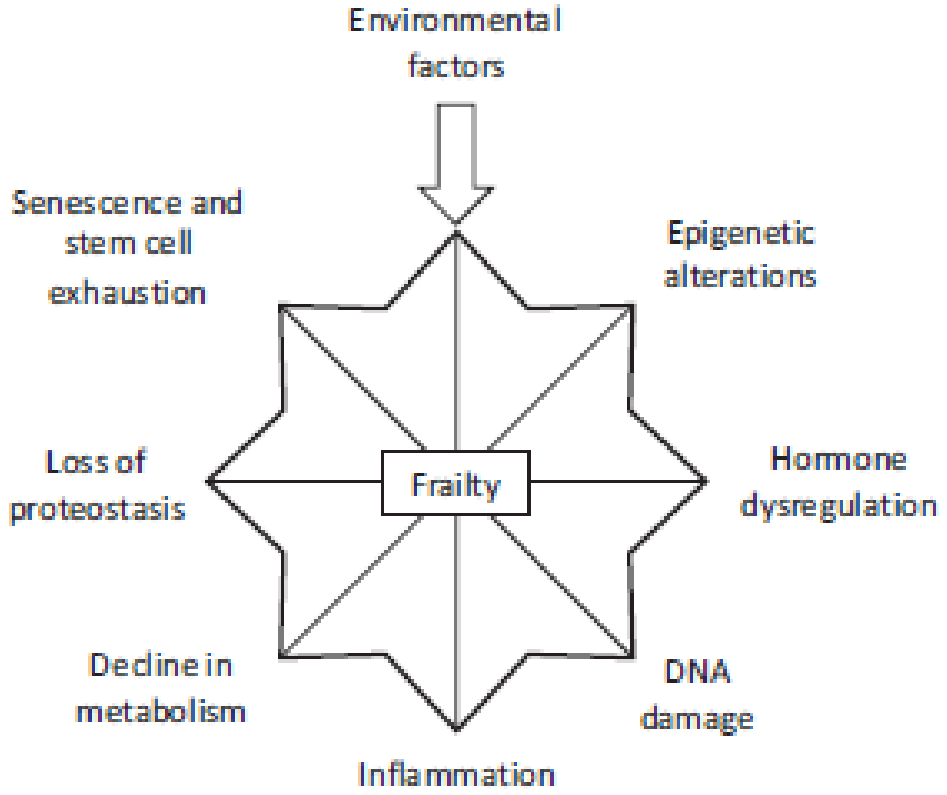


FIGURE 1 Schematic diagram that illustrates putative frailty mechanisms. Potential frailty mechanisms are interrelated and modified by environmental factors. Modified from concepts proposed as the hallmarks of aging[12] and the pillars of aging[13]

Bissel and Howlett, Aging Medicine, 2019

Blood biomarkers of frailty

- Should detect frailty before it is clinically advanced
- Should be a risk factor common to all age-related diseases
- Should also predict mortality
- Should also related to biologic aging mechanisms

- Candidates?

Zampino, Exp Gerontology, 2020

Biomarkers of frailty

- Is frailty a state of dysregulated inflammation due to cellular senescence?

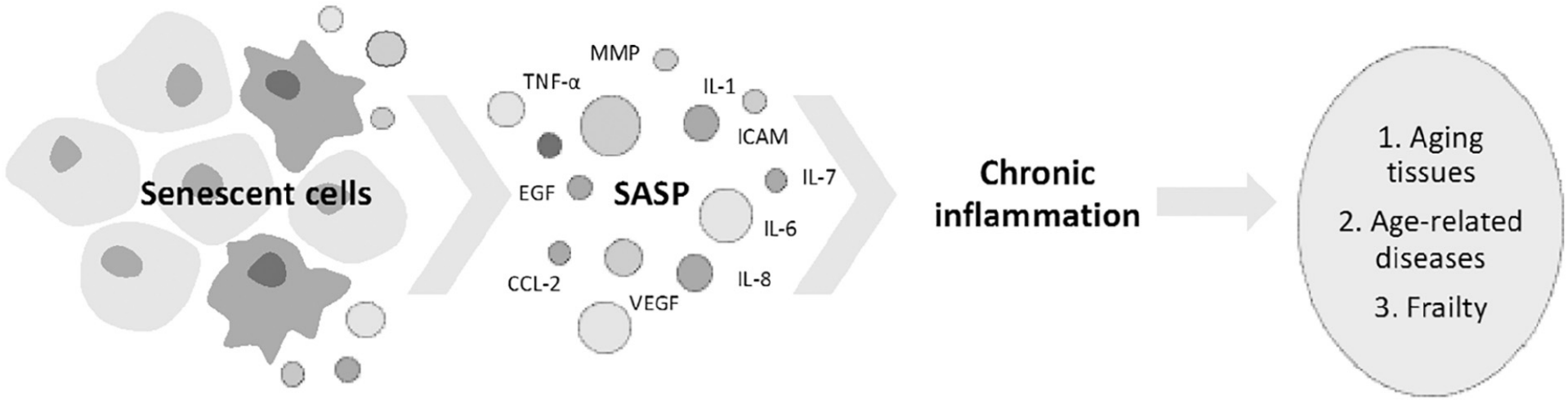
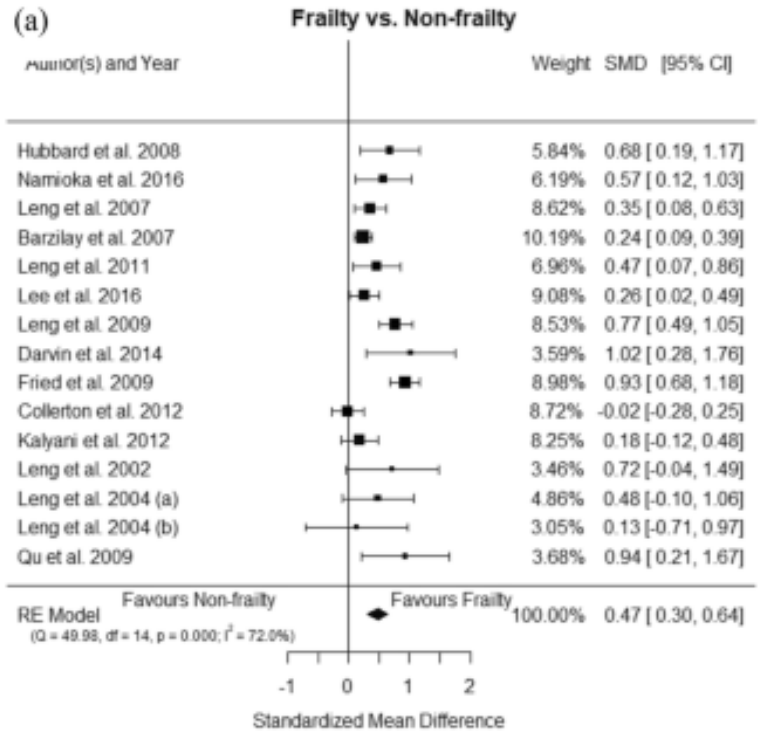
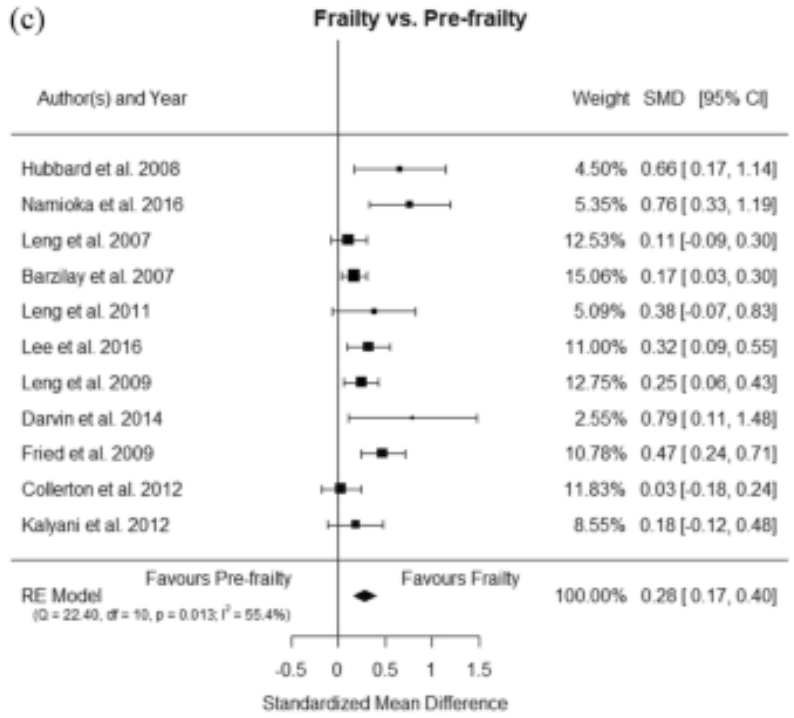


Fig. 1. Hypothesized mechanism by which senescent cells contribute to age-related conditions. Senescent cells produce the Senescence-Associated Secretory Phenotype (SASP), rich in inflammatory molecules, which in turn induces aging of the tissues and age-related diseases. TNF-α, tumor necrosis factor-α; MMP, matrix metalloproteinases; IL-1, interleukin-1; ICAM, intracellular adhesion molecules; IL-7, interleukin-7; IL-6, interleukin-6; IL-8, interleukin-8; VEGF, vascular endothelial growth factor; CCL-2, chemokine (C—C motif) ligand 2; EGF, endothelial growth factor.

Inflammation and frailty

- Numerous studies in humans link elevated IL-6 to frailty as well as physical disability





Other cytokines are also related including TNF-SR and IL-10 as well as CRP

Forest plots of IL6 concentration **a** frailty vs. non-frailty groups; **c** frailty vs. pre-frailty groups

Marcos-Pérez, Diego, et al. GeroScience (2020): 1-23.

Epigenetics and frailty

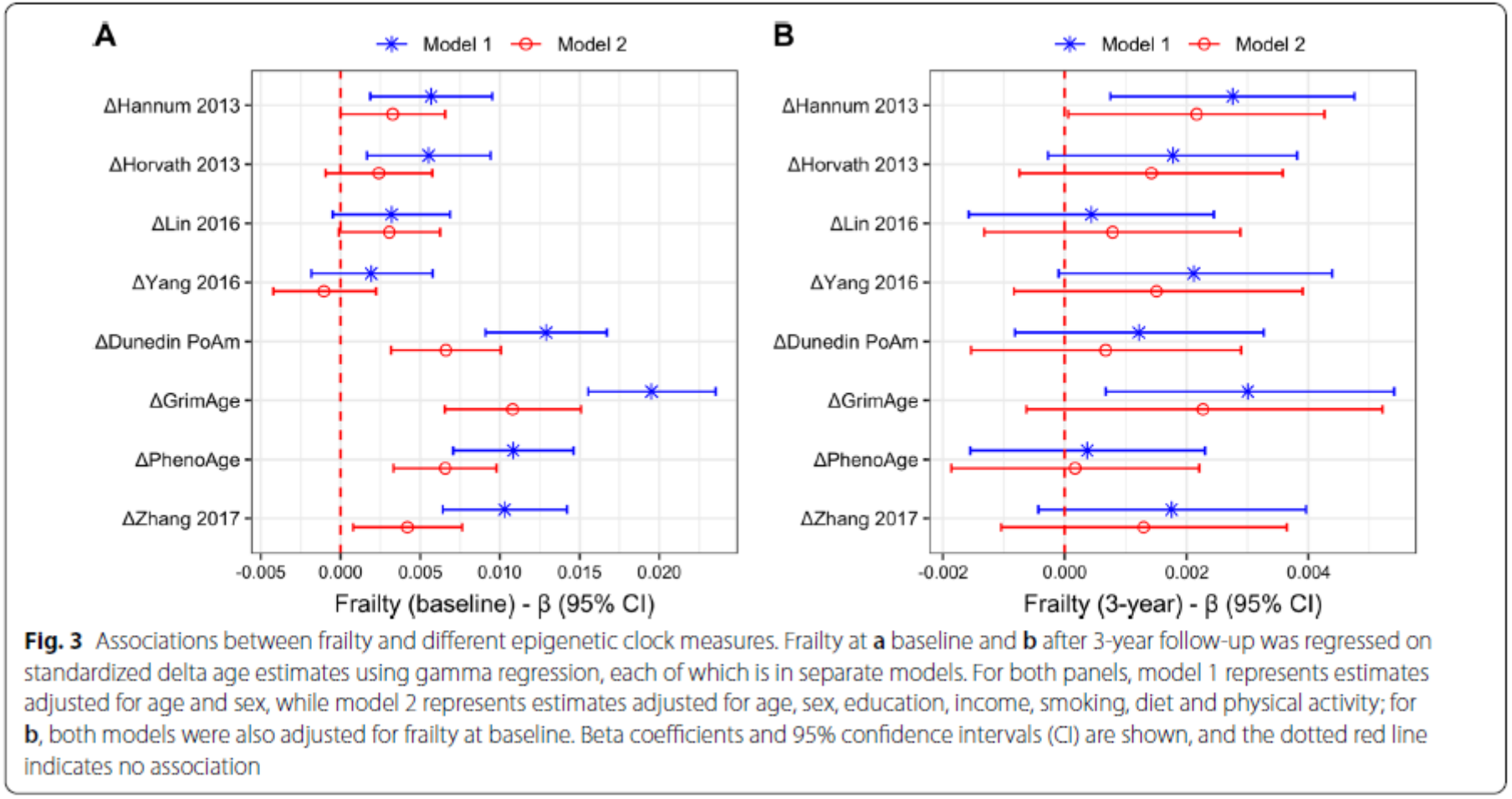


Fig. 3 Associations between frailty and different epigenetic clock measures. Frailty at **a** baseline and **b** after 3-year follow-up was regressed on standardized delta age estimates using gamma regression, each of which is in separate models. For both panels, model 1 represents estimates adjusted for age and sex, while model 2 represents estimates adjusted for age, sex, education, income, smoking, diet and physical activity; for **b**, both models were also adjusted for frailty at baseline. Beta coefficients and 95% confidence intervals (CI) are shown, and the dotted red line indicates no association

Verschoor, C.P., Lin, D.T.S., Kobor, M.S. *et al.* Epigenetic age is associated with baseline and 3-year change in frailty in the Canadian Longitudinal Study on Aging. *Clin Epigenet* **13,** 163 (2021). https://doi.org/10.1186/s13148-021-01150-1

Metabolomics and frailty

- Frail individuals characterized by alterations in metabolic pathways
  - Rattray NJW, Nature Communications 2019
  - Marron MM, Metabolites, 2019
  - Westbrook R, JGBS, 2021
- Implicate TCA cycle, lipid metabolism, mitochondrial function

- Metabolomic age?
  - Robinson O, Aging Cell, 2020

Mitochondrial copy number and frailty

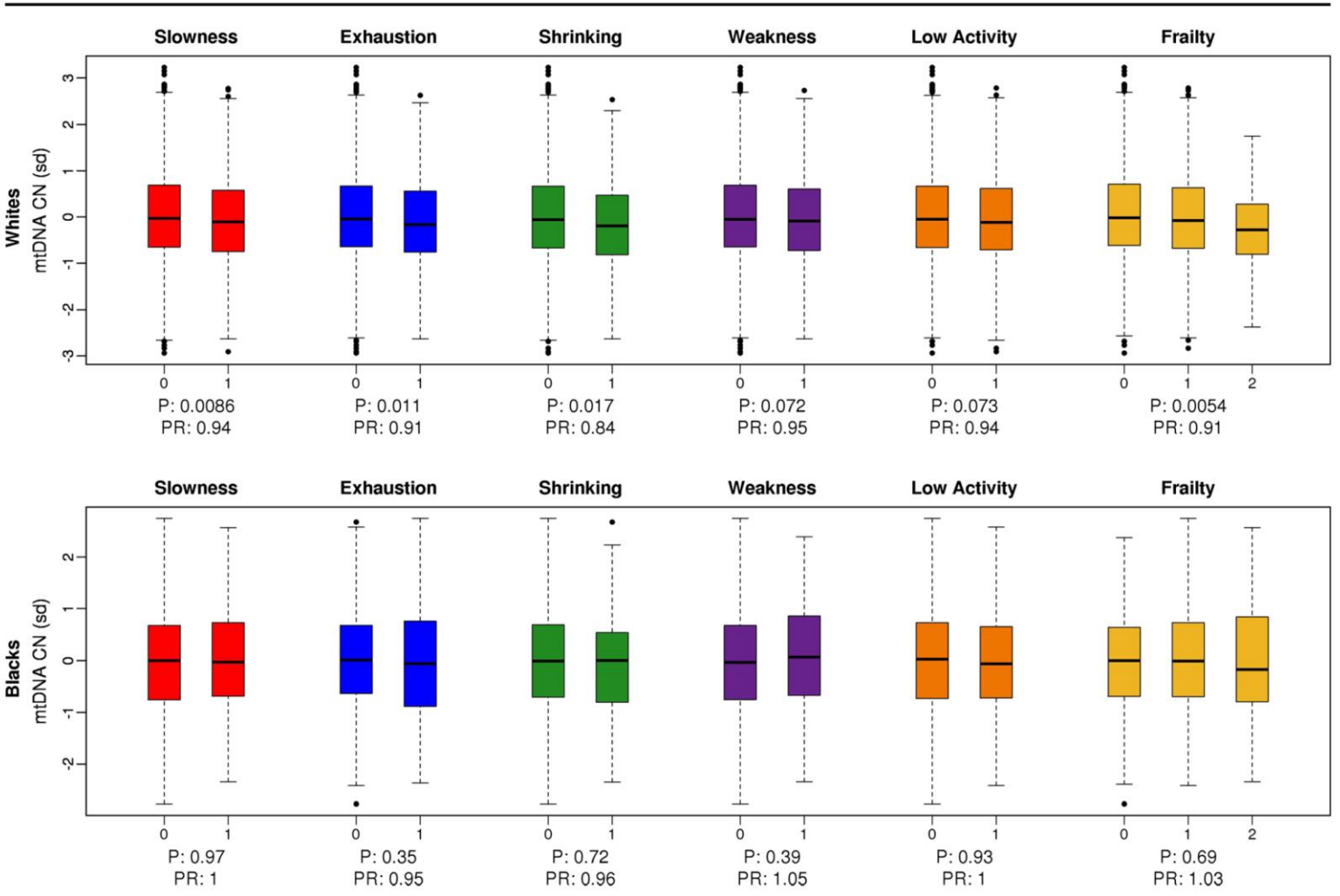


Fig. 1 Frailty components in CHS. Association between age-, sex-, and collection site-adjusted mitochondrial copy number and frailty components in white samples (*top panel*) and black samples (*bottom* not at risk (0) for each characteristic of frailty. Overall frailty was scored in terms of number of characteristics that each participant was at risk for (robust (0 characteristics), pre-frail (1–2 characteristics), and frail (≥2

Ashar, Foram N., et al. "Association of mitochondrial DNA levels with frailty and all-cause mortality." *Journal of molecular medicine* 93.2 (2015): 177-186.

Interventions to ameliorate frailty and improve physical function

- Physical activity
  - Inconsistent results for frailty (Trombetti A, Ann Int Med, 2018)
  - Improves physical function and prevents major mobility disability (Pahor M, JAMA, 2014)
- Diet
  - Caloric restriction (mostly animal studies), Mediterranean diet (Kojima G, JAGS, 2018)
  - Weight loss improved function in obese
- Multicomponent diet, exercise, etc.
  - Reduced frailty phenotype and prevented decline in physical function (Cameron, BMC Medicine, 2013, Fairhall, BMJ Open, 2015)
- Omega-3 fatty acids
  - No improvement in 400 meter walk or IL-6 levels (Pahor, JGMS 2020)
- Resveratrol
  - Reduced frailty index scores in mice (Kane AE, JGBS, 2018)
- ACE inhibitor
  - Frailty index scores reduced in mice with enalapril for 9 months (Keller K, JGBS, 2018)

Interventions to ameliorate frailty and improve physical function

- Testosterone Trials
  - Some increase in physical function and components of vitality in men with low T (Snyder P, Endo reviews, 2018)
- Senolytics
  - Mice – intermittent administration of dasatinab and quercetin to senescent cell-transplanted young mice and naturally old mice increased survival by 36% and alleviated physical function impairment (Xu M, Nature Medicine, 2018)
  - People – Open label D + Q study in people with IPF improved physical function, but not FI-LAB (Justice J, EBioMed 2019)
- Metformin
  - Trial underway in older adults with pre-diabetes (Espinoza S, JGMS, 2020)
  - Targeting Aging with Metformin (TAME) - Multimorbidity outcome
- Aspirin
  - ASPREE study, 100 mg of aspirin did not reduce incident disability, frailty phenotype or frailty index, may have reduced persistent disability (Woods R JGMS, 2020; Espinoza S, JGMS, 2021)
- Lomecel-B
  - Mesenchymal Signaling Cell formulation, phase 2B
  - 6 min walk is primary outcome (Yousefi, J Frailty and Aging, 2022)

Moving Frailty Toward Clinical Practice: NIA Intramural Frailty Science Symposium Summary

Jeremy Walston, MD, Karen Bandeen-Roche, PhD,† Brian Buta, MHS,* Howard Bergman, MD,‡ Thomas M. Gill, MD,§ John E. Morley, MD,¶ Linda P. Fried, MD,‖ Thomas N. Robinson, MD,** Jonathan Afilalo, MD,†† Anne B. Newman, MD,‡‡ Carlos López-Otín, MD,§§ Rafa De Cabo, PhD,¶¶ Olga Theou, MD,‖‖ Stephanie Studenski, MD,¶¶ Harvey J. Cohen, MD,*** and Luigi Ferrucci, MD, PhD¶¶*

RECOMMENDATIONS

- Refine definitions and language about frailty
- Demonstrate that frailty is modifiable in clinical trials
- Continue to tailor care using frailty and physical function to target patients at risk
- Integrate biology of aging with frailty
- Develop deeper understanding of system dynamics most important in frailty that can be targeted to improve resilience

Walston, Jeremy, et al. "Moving frailty toward clinical practice: NIA intramural frailty science symposium summary." Journal of the American Geriatrics Society 67.8 (2019): 1559-1564.

Research directions (1)
Further refine frailty and physical function as outcomes

- Progress
  - Whole person phenotype summarizes risks and benefits
  - Person-centered outcomes, focus on health span
- Issues
  - Objective physical function assessments are not part of clinical practice
  - Disability often self-reported- not objective
  - Frailty phenotype includes weight loss and physical activity which might be part of the intervention
  - Frailty index includes many chronic diseases which might not be reversible
- Approaches
  - Refine measures for sensitivity to intervention
  - Develop “Resilience tests”
    - Direct measures of the ability to tolerate stress
      - Treadmill test
      - Stress hormone responses
      - Evidence of ability to recover from clinical stress such as surgery
  - Validate of personal monitoring as physical function measures

Research directions (2)
Therapeutics

- Progress
  - Many trials developing with frailty and function as outcomes
  - Frailty is now an FDA designated condition
- Issues
  - Uncertainty about tissue specificity of aging biologic processes
  - Disease-specific therapies often do not address frailty and physical function as outcomes
- Approaches
  - Studies targeting underlying biology of aging should include frailty assessments, physical performance tests, self-reported function and quality of life as outcomes
  - Use physical activity benefit as target effect size to beat

Research Directions (3) Systems approaches

- Signaling between systems
  - Direct contact
  - Signaling molecules
    - Paracrine
    - Endocrine
  - Extracellular vesicles

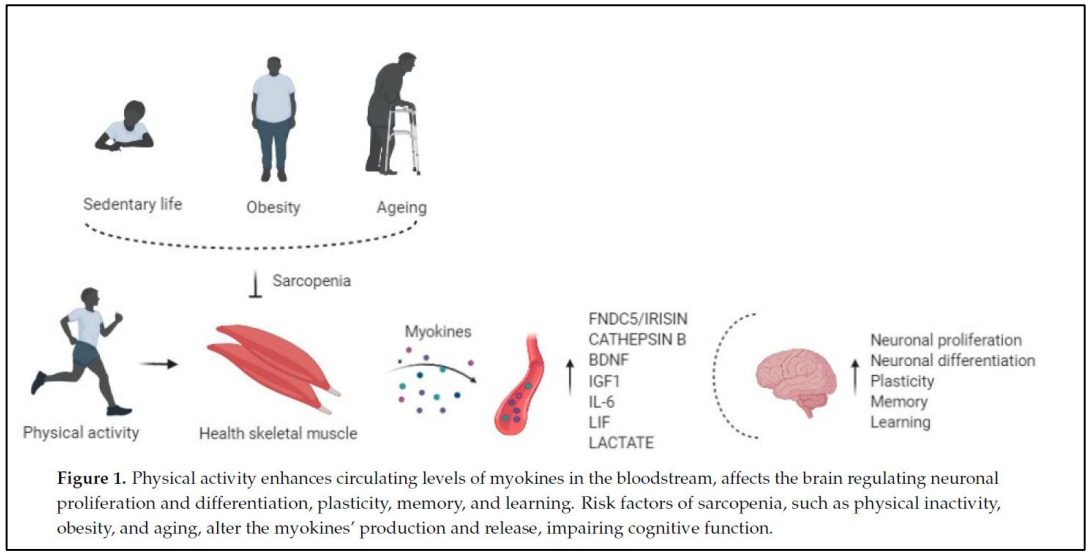
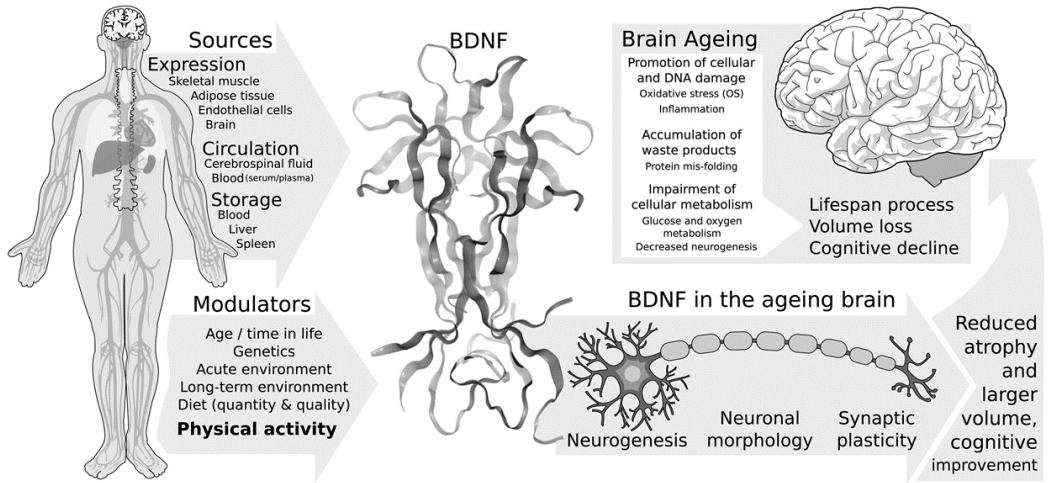


Figure 1. Physical activity enhances circulating levels of myokines in the bloodstream, affects the brain regulating neuronal proliferation and differentiation, plasticity, memory, and learning. Risk factors of sarcopenia, such as physical inactivity, obesity, and aging, alter the myokines' production and release, impairing cognitive function.



Walsh, Erin I., et al. "Towards an understanding of the physical activity-BDNF-cognition triumvirate: A review of associations and dosage." Ageing research reviews 60 (2020): 101044.

Kim, Sujin, et al. "Roles of myokines in exercise-induced improvement of neuropsychiatric function." Pflügers Archiv-European Journal of Physiology 471.3 (2019): 491-505.

Scisciola, Lucia, et al. "Sarcopenia and cognitive function: Role of myokines in muscle brain cross-talk." Life 11.2 (2021): 173.

Mustapic, Maja, et al. "Plasma extracellular vesicles enriched for neuronal origin: a potential window into brain pathologic processes." Frontiers in neuroscience 11 (2017): 278.

Frailty and function - Summary

- Physiologic integration
- Linked to more distal clinical outcomes
- Growing evidence of biologic aging underpinnings

Is frailty = aging?

Acknowledgements

- NIA
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