



# Frailty and Ageing: How did we get here? Where are we going?

Duke-NUS Centre for Ageing Research & Education  
May 3<sup>rd</sup>, 2026

Benjamin Seligman, MD, PhD

Division of Geriatric Medicine, Department of Medicine  
David Geffen School of Medicine at UCLA

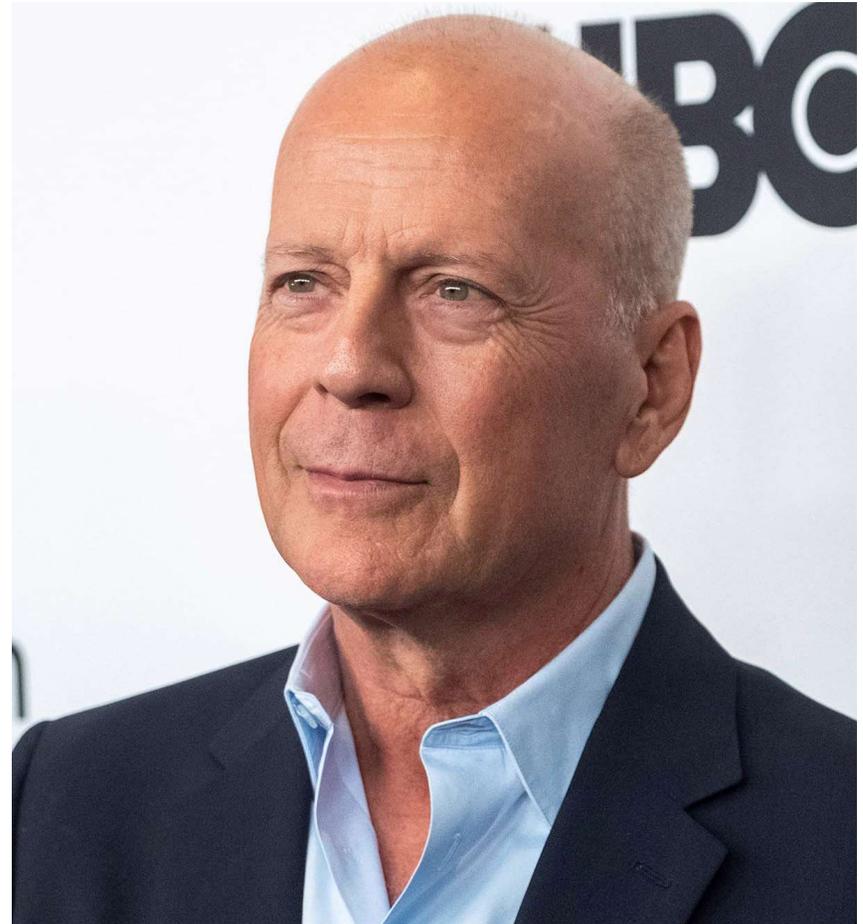


I am a consultant for Ceresti Health

1. Describe the history of frailty and measuring aging
2. Explain the relationship between frailty and health outcomes
3. Describe the uses of frailty and areas of uncertainty
4. Describe opportunities for deepening our understanding of frailty and aging



Adapted from James Manning/PA Images via Getty



Charles Sykes/Invision/AP

## Three Things We Believe About Ageing:

1. We can measure it
2. It has prognostic value
3. It has decision-making value

# Can We Measure Frailty?

The obvious characteristics of senility are evidenced in the appearance, attitude, gait, mentality and the tout ensemble of mental and physical decay.

The irregularity in the order and the wide variations in time and extent of the senile changes in different individuals make it impossible to establish a norm or standard for these changes.

Nascher, Ignatz Leo. *Geriatrics*. 1914.

TABLE 2. CORRELATION COEFFICIENTS BETWEEN AGE AND EACH OF SEVENTEEN TESTS AND SELECTION FOR AGING BATTERY

Test	Test item	Sample size	Correlation with age
1	Hair graying score	442	+ .717
2*	Skin elasticity	433	+ .604
3*	Systolic blood pressure	437	+ .519
4	Diastolic blood pressure	437	+ .409
5	Heart size	380	+ .294
6	Thorax size	380	-.124
7*	Total vital capacity	429	-.402
8	Tidal volume	428	—
9	One-second expiratory volume	429	-.126
10*	Hand grip strength	437	-.323
11*	Light extinction test	435	+ .488
12*	Vibrometer	437	+ .537
13*	Visual acuity	433	-.423
14	Audiometry at 200 cycle/sec.	437	+ .445
15*	Audiometry at 4,000 cycle/sec.	436	+ .596
16*	Serum cholesterol	426	+ .234
17	Total serum albumin	169	-.267

\* Selected.

Hollingsworth, Hashizume, Jablon. *Yale J Biol Med* 1965.

DRAFT TEST BATTERY FOR PHYSIOLOGICAL AGE IN MAN

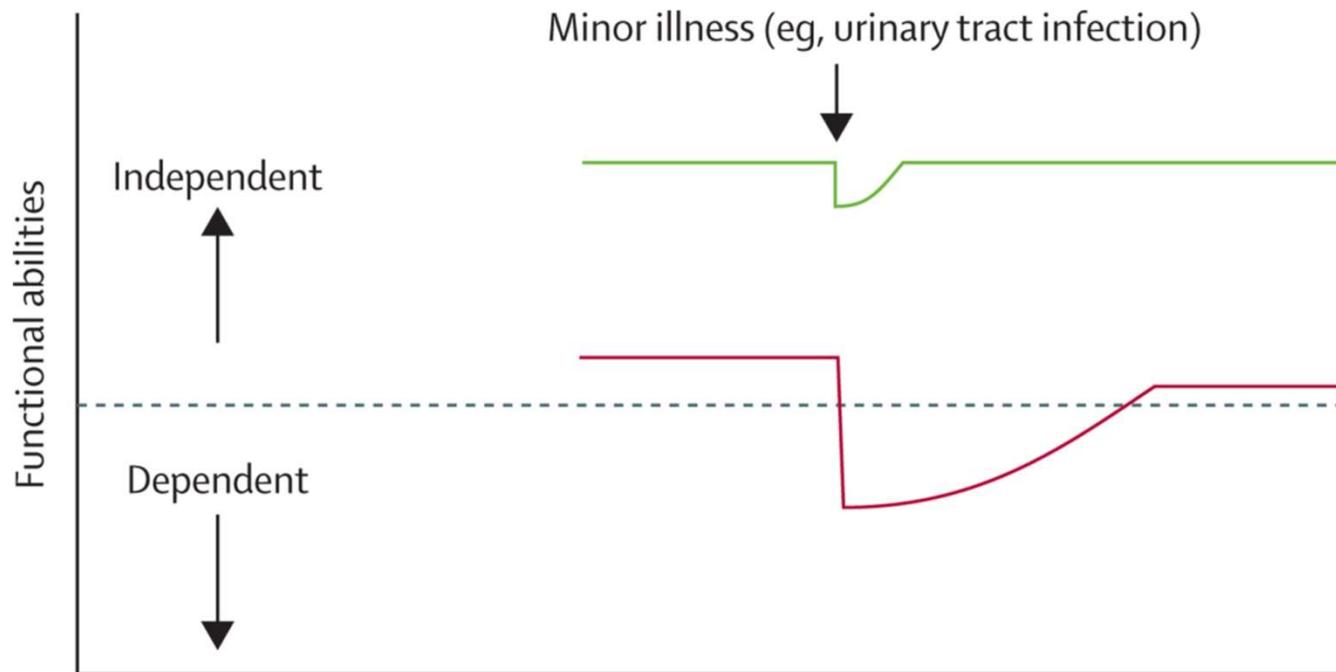
Test	Reference	r
Hair-graying score	1	0.717
(a) Skin elasticity	1	0.604
(a, b) Systolic blood-pressure	1	0.519
(b) Diastolic blood-pressure	1	0.409
(b) Heart size	1	0.294
(b) Thorax size	1	-0.124
(a, b) Total vital capacity	1	-0.402
(b) Tidal volume	1	..
(b) One-second expiratory volume	1	-0.126
(a) Hand-grip strength	1	-0.323
(a) Light extinction test	1	0.488
(a) Vibrometer	1	0.537
(a, b) Visual acuity	1	-0.423
(b) Audiometry (200 c.p.s.)	1, 35	0.445
(a, b) Audiometry (4000 c.p.s.)	1, 35	0.596
(a, b) Serum-cholesterol	1, 31, 32	0.234
(b) Total serum-albumin	1	-0.267
(b) Albumin/globulin ratio	16	..
(b) Plasma water	36	..
(b) Mean venous pressure	16	..
(b) Protein-bound iodine	31	-0.33
Serum-copper	17	..
Serum-elastase	37	..
Serum-r.n.a.ase	38	..
Nail calcium content	15	..
(b) Stature	21, 39	-0.532
(b) Seated stature	21	-0.53
(b) Trunk height	21	-0.34
Biacromial diameter	21	-0.40
Metacarpal osteoporotic index	39	-0.786
Lymphocyte r.n.a./d.n.a. ratio	10	..
• Explant latency	40, 41	..
• Serum growth-promotion (tissue-culture)	42-45	..
• Biopsy healing/contraction	46-48	..
• Clonal further viability	49-51	..
• Leucocyte aneuploidy	52	..
• Autoantibody titres	18-20	..
• Skin melanocyte-count	13, 14	..
w.a.i.s. tests (automated set)	9, 22, 31, 35	..
Similarities	..	..
Digit span	..	..
Vocabulary	..	..
Digit symbol	..	..
Block design	..	..
Digit copying	..	..
Tapping test	35	-0.44
Reaction-time, ruler test	35	0.48
Reaction-time, light	35	0.35
Flicker-fusion frequency	35	-0.48
Taste sensitivity	53	..
† Total 5-year mortality	..	..
† Organ weights	54	..
† Disease-specific mortalities	..	..
(b) † Tumour incidence, living	..	..
† Tumour incidence, necropsy	..	..
† Amyloidosis, stainable	..	..
† Lipofuscin accumulation	55	..
† Aortic calcium	16, 56	..
† Collagen contractility	..	..
† Collagen fluorescence	57	..

Comfort. *Lancet* 1969

- “The frail elderly are individuals, over 65 years of age, dependent on others for activities of daily living, and often in institutional care.”<sup>1</sup>
- “Patients most likely to benefit from geriatric care are likely to be frail, which implies increased susceptibility to adverse health events, increased need for health care to maintain physical and mental functioning, and high likelihood of needing long-term care.”<sup>2</sup>
- “...there is now an appreciation that many manifestations of frailty are observed in conditions where a metabolic balance seems to be impaired; for example, cytokines are overexpressed in immune disorders, in inflammatory states, and in debilitating conditions and hormonal mediators are deficient...”<sup>3</sup>
- “In fact, no rigorous explanation has been advanced. Frailty lacks a conceptual framework.”<sup>4</sup>

1. Woodhouse KW *et al.* *Q J Med.* 1988;68(255):505-506.
2. Winograd CH. *J Am Geriatr Soc.* 1991;39(9 Pt 2):25S-35S.
3. Hamerman D. *Ann Intern Med.* 1999;130(11):945-950.
4. WM 2nd. *J Am Geriatr Soc.* 1993;41(9):1004-1008.

“Frailty is a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of poor outcomes...”



Clegg A, Young J, Iliffe S, *et al. Lancet.* 2013;381(9868):752-762.

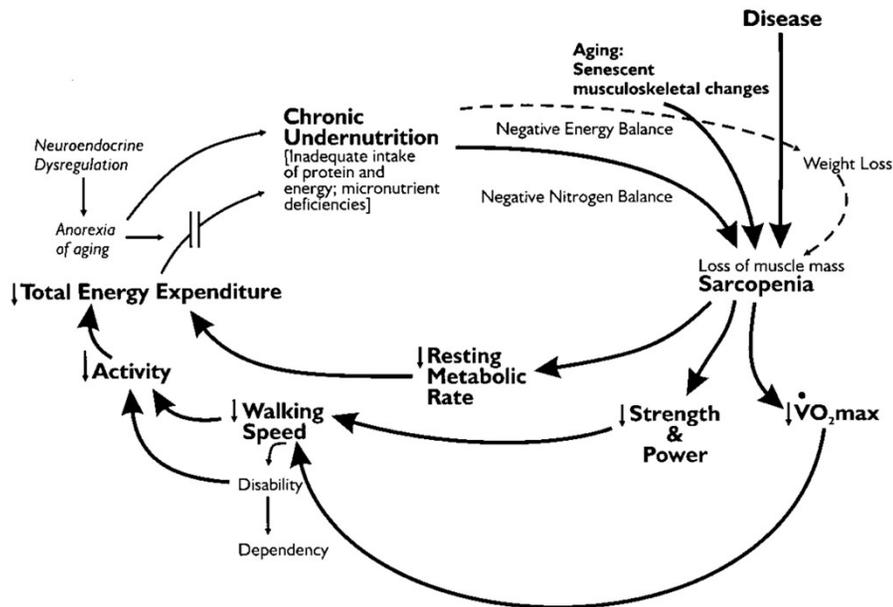
“Frailty is a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of poor outcomes...”

## Ministry of Health Definition of Frailty:

Frailty is a dynamic and evolving state of health which involves the gradual loss of physiological in-built reserves leading to losses in one or more domains of human function (physical, cognitive, psychological and/or social) and increases the vulnerability of older adults to adverse health-related outcomes.

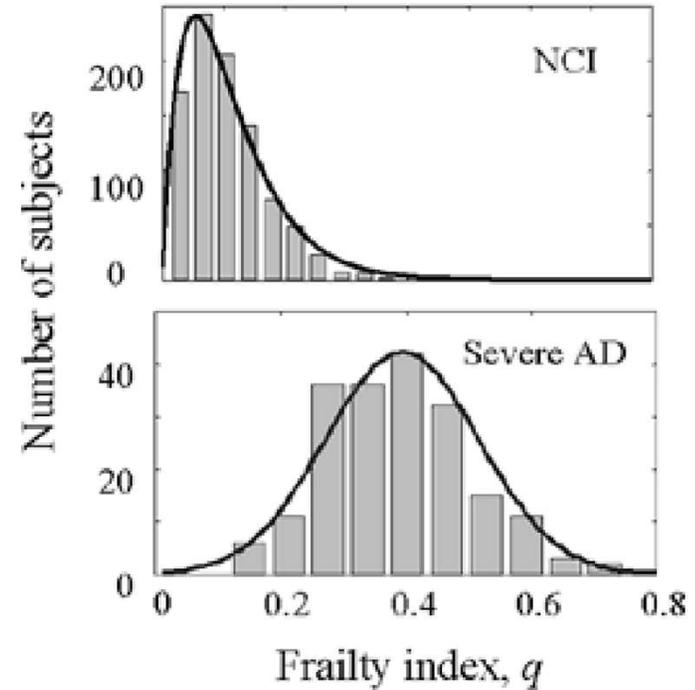
Frailty can be prevented, reversed, or delayed in the early stages and managed in the later stages, through early detection and interventions to optimise functional ability, activity participation and quality of life.

## Physical Frailty



Fried et al. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-M156.

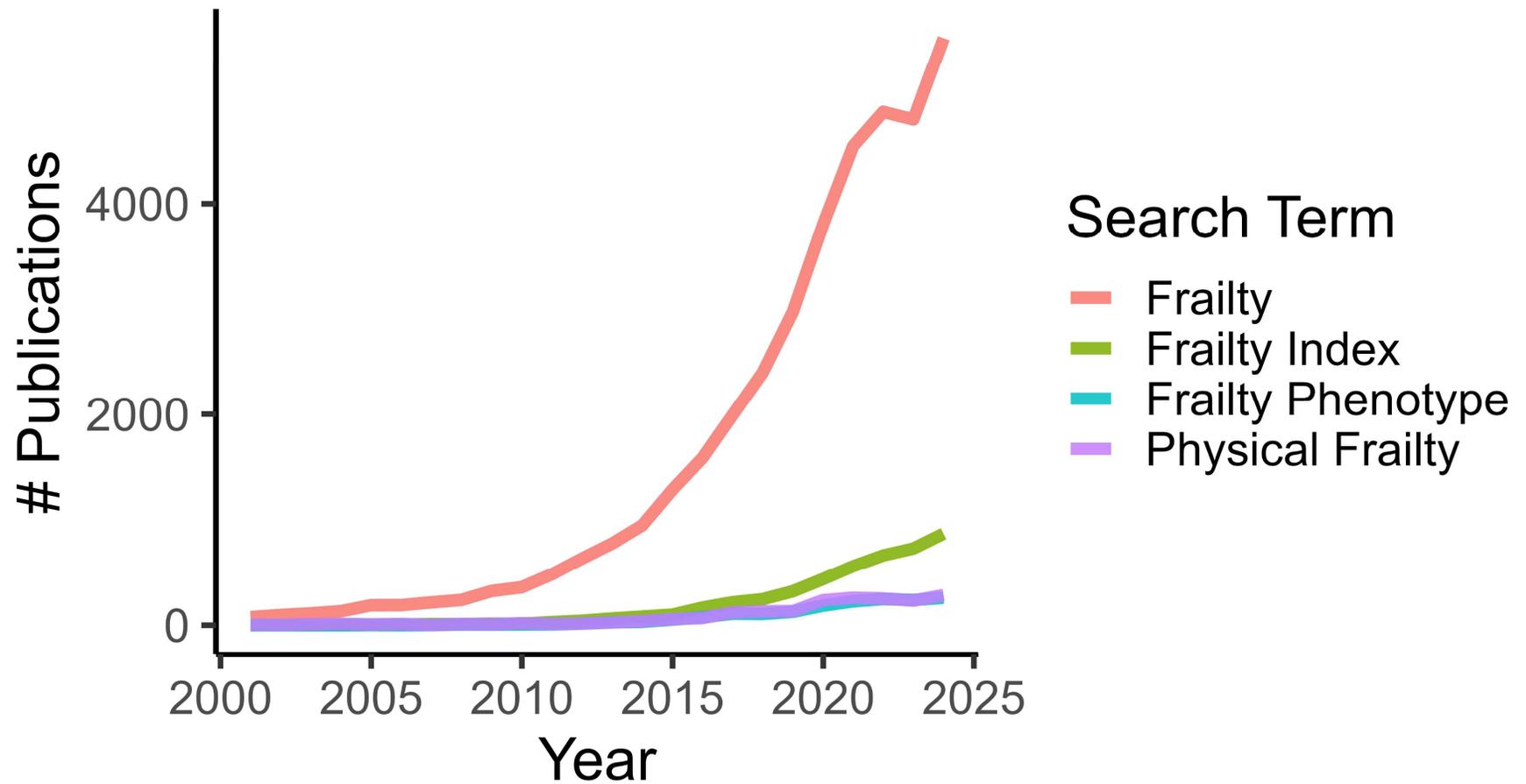
## Deficit Accumulation Frailty



Mitnitski AB, Mogilner AJ, Rockwood K. *ScientificWorldJournal.* 2001;1:323-336.

- Close relationship between inflammation and frailty<sup>1</sup>
- Frailty associated with mtDNA copy number and mitochondrial function with activity<sup>2,3</sup>
- Associations between frailty and ‘biological age’
  - Epigenetic Age Acceleration<sup>4</sup>
  - Proteome Age<sup>5</sup>

1. Ferrucci L, Fabbri E. *Nat Rev Cardiol*. 2018;15(9):505-522.
2. Ashar FN et al. *J Mol Med (Berl)*. 2015;93(2):177-186.
3. Lewsey SC et al. *JCI Insight*. 2020;5(20):e141246.
4. McCrory C et al. *J Gerontol A Biol Sci Med Sci*. 2021;76(5):741-749.
5. Argentieri MA et al. *Nat Med*. 2024;30(9):2450-2460



### **Physical Frailty**

- Fried Frailty Phenotype
- Study of Osteoporotic Fractures
- Short Physical Performance Battery
- Gait Speed
- Timed Up And Go
- Chair Rises
- Grip Strength

### **Specialty-Specific**

- Risk Analysis Index (surgery)
- Essential Frailty Toolset (AVR)
- G-8 (chemotherapy for solid tumors)
- Myeloma Frailty Score (MM)
- Liver Frailty Index (ESLD)

### **Deficit Accumulation Frailty**

- Rockwood Frailty Index
- Kihon Checklist
- Veterans Affairs Frailty Index
- NHS England eFI
- Atrium Health eFI
- Kim Claims-Based Frailty Index

### **Other**

- Edmonton Frailty Scale
- Groningen Frailty Indicator
- Tilburg Frailty Indicator
- Vulnerable Elder Survey-13
- PRIMSA-7
- FRAIL Scale
- Clinical Frailty Scale

# The Clinical Frailty Scale

## CLINICAL FRAILTY SCALE

	<b>1</b>	<b>VERY FIT</b>	People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
	<b>2</b>	<b>FIT</b>	People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g., seasonally.
	<b>3</b>	<b>MANAGING WELL</b>	People whose medical problems are well controlled, even if occasionally symptomatic, but often not regularly active beyond routine walking.
	<b>4</b>	<b>LIVING WITH VERY MILD FRAILTY</b>	Previously "vulnerable" this category marks early transition from complete independence. While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up" and/or being tired during the day.
	<b>5</b>	<b>LIVING WITH MILD FRAILTY</b>	People who often have more evident slowing, and need help with high order instrumental activities of daily living (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
	<b>6</b>	<b>LIVING WITH MODERATE FRAILTY</b>	People who need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
	<b>7</b>	<b>LIVING WITH SEVERE FRAILTY</b>	Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).
	<b>8</b>	<b>LIVING WITH VERY SEVERE FRAILTY</b>	Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
	<b>9</b>	<b>TERMINALLY ILL</b>	Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise living with severe frailty. Many terminally ill people can still exercise until very close to death.

### SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.  
In severe dementia, they cannot do personal care without help.  
In very severe dementia they are often bedfast. Many are virtually mute.

Clinical Frailty Scale ©2005-2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: [www.geriatricresearch.ca/rockwood](http://www.geriatricresearch.ca/rockwood) K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

# Clinical Frailty Scale

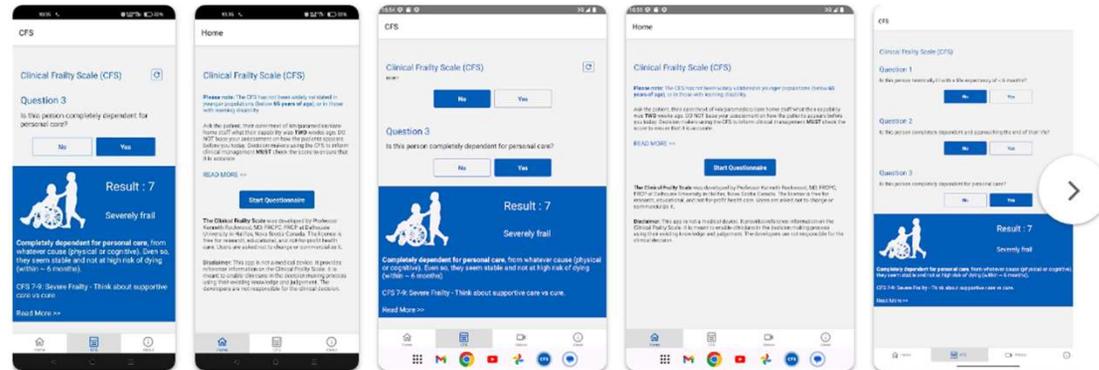
Electronic MAR

1K+ Downloads | Everyone

Install

Share | Add to wishlist

This app is available for your device



**Why Measure Frailty**

**Help Me Choose a Frailty  
Tool**

**Overview of Frailty Tools**

**Clinical Frailty Scale**

**CGA-FI Calculator**

**Risk Analysis Index**

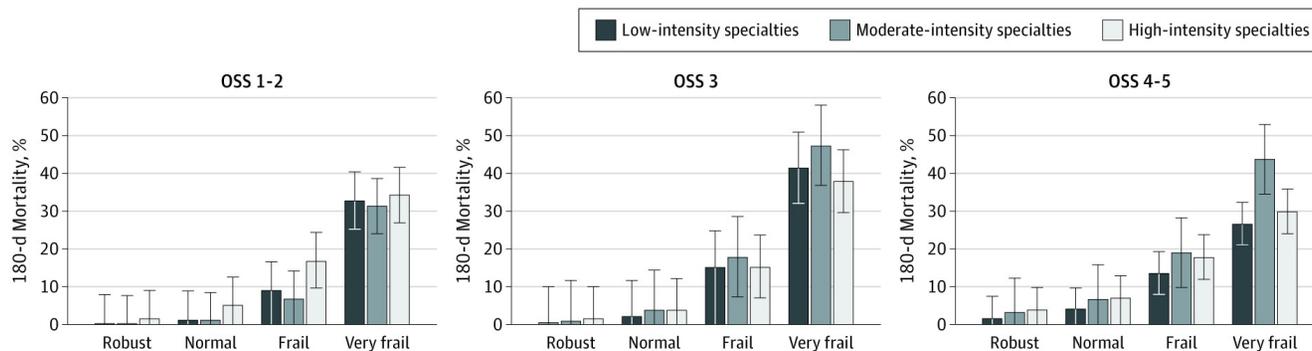
**Frailty Phenotype**

**FRAIL Scale**

<https://efrailty.hsl.harvard.edu/>

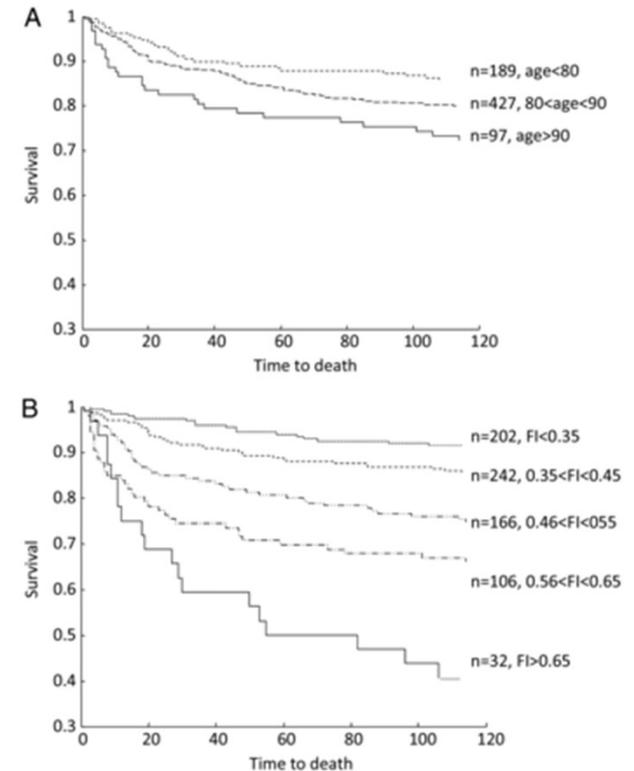
# Does Frailty Have Prognostic Value?

- Meta-analyses differ in association between frailty & surgical outcomes based on specialty/procedure
  - May be variability in meta-analysis methods/quality
- In general, frailty tied to greater risk of perioperative mortality and surgical complications<sup>1</sup>



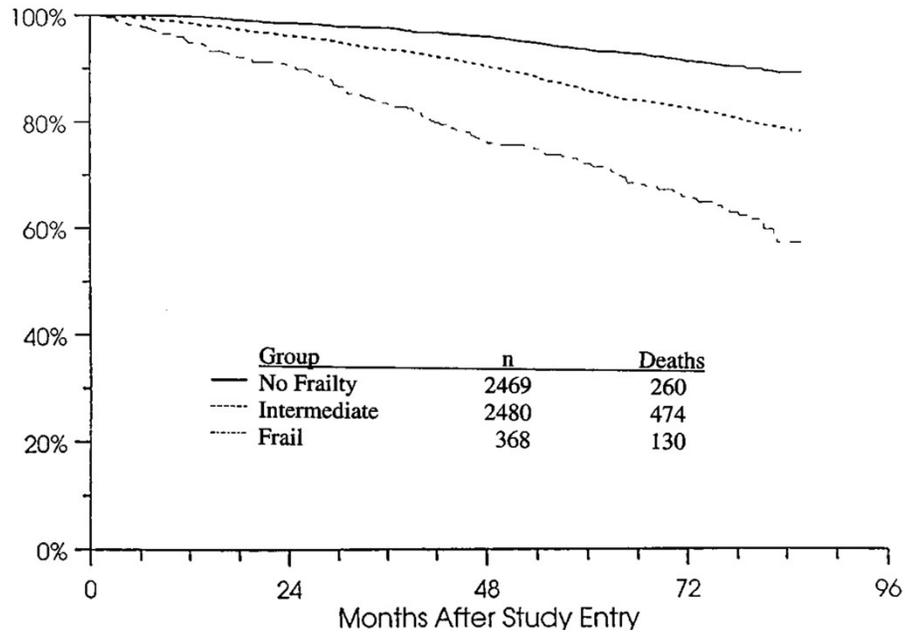
1. George EL, Hall DE, Youk A, et al. JAMA Surg. 2021;156(1):e205152.

- Multiple instruments had high sensitivity but low specificity for mortality, ADL worsening, and falls<sup>1</sup>
- Frailty index from admission CGA was associated with mortality and LOS<sup>2</sup>
- A 31-item laboratory + vital signs frailty measure was associated with mortality, LOS, ICU transfer, and nursing home placement<sup>3</sup>

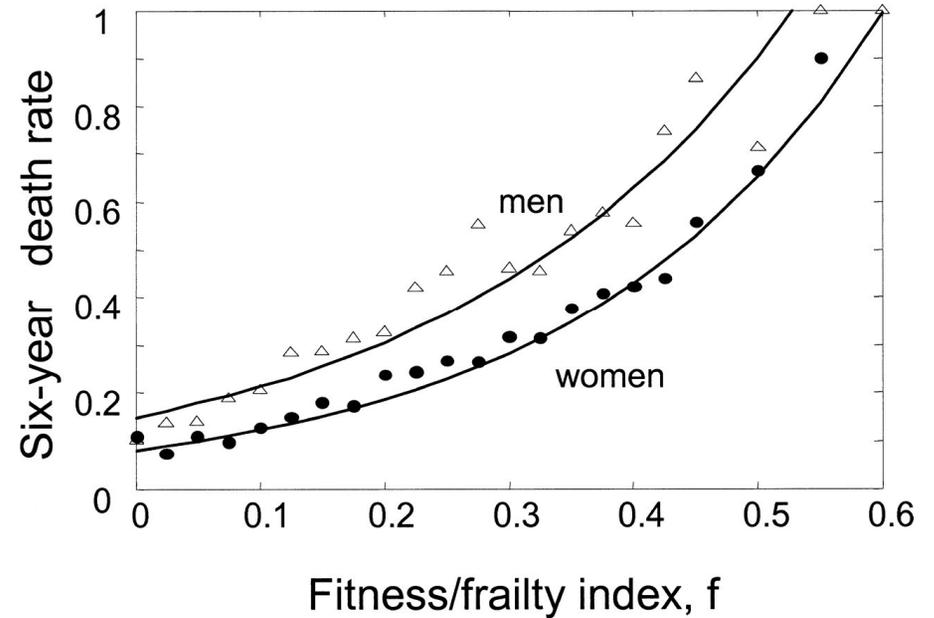


1. Oviedo-Briones M, et al. *J Cachexia Sarcopenia Muscle*. 2022;13(3):1487-1501.
2. Evans SJ, Sayers M, Mitnitski A, Rockwood K. *Age Ageing*. 2014;43(1):127-132.
3. Ysea-Hill O, Gomez CJ, Mansour N, et al. *J Am Geriatr Soc*. 2022;70(11):3163-3175.

## Frailty in the Community



Fried *et al.* *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-M156.

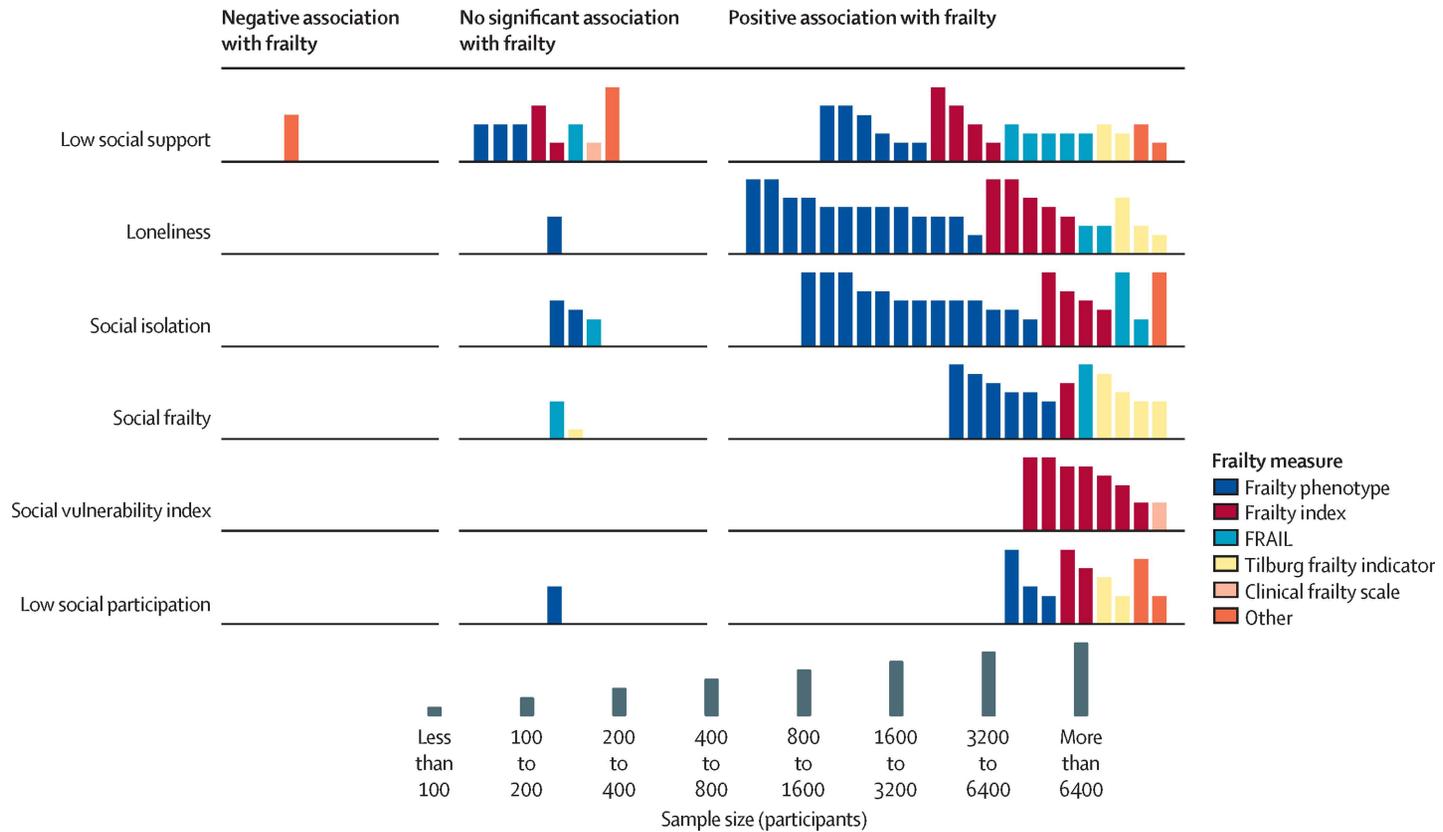


Mitnitski AB, Song X, Rockwood K. *J Gerontol A Biol Sci Med Sci.* 2004;59(6):M627-M632.

- Frailty is associated with increased risk of falls<sup>1</sup>
- Frailty and pre-frailty associated with transition to nursing home<sup>2</sup>
- Review of 5 meta-analyses found consistent association between frailty & all-cause mortality<sup>3</sup>

1. Yang ZC, Lin H, Jiang GH, et al. *J Nutr Health Aging*. 2023;27(6):487-595.
2. Kojima G. *J Geriatr Phys Ther*. 2018;41(1):42-48.
3. Ekram ARMS, Woods RL, Britt C, et al. *J Frailty Aging*. 2021;10(4):320-326.

# Frailty and Social Vulnerability



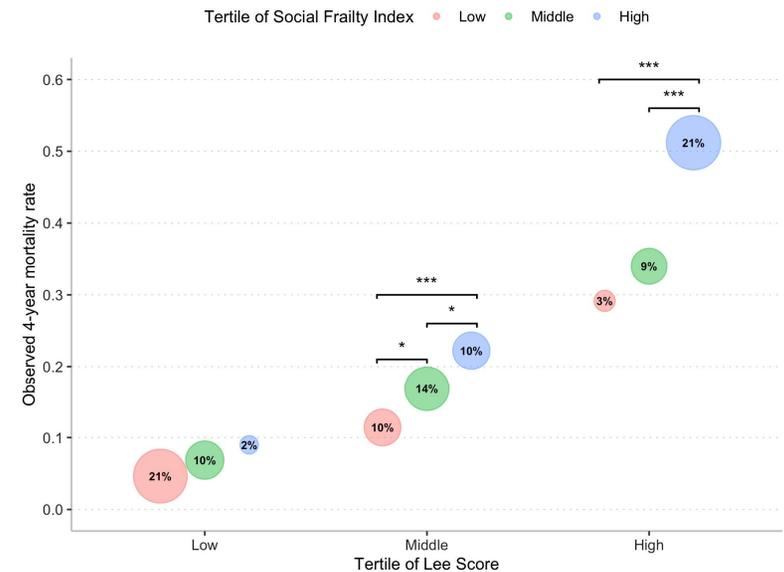
Hanlon P, Wightman H, Politis M, et al. *Lancet Healthy Longev.* 2024;5(3):e214-e226.

Identifying areas of vulnerability (sometimes) outside of the body

Significantly associated with mortality & functional limitations<sup>1,2,3</sup>

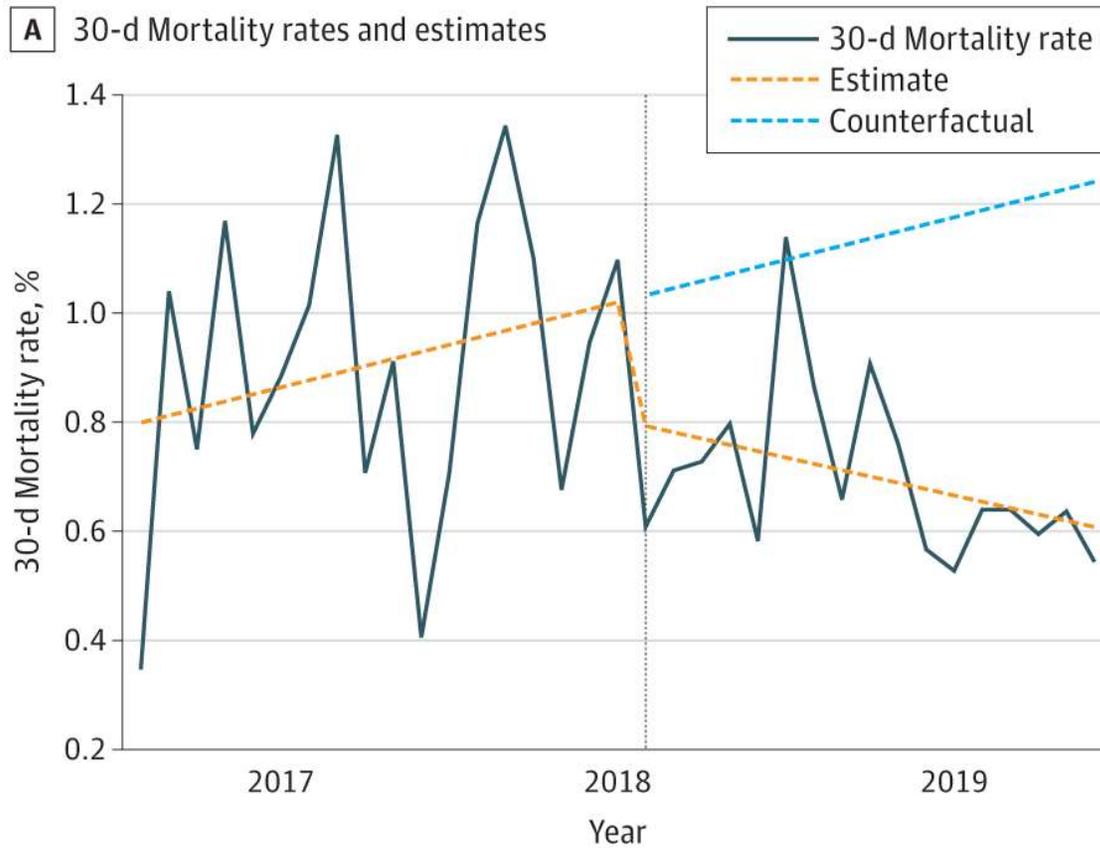
Little consensus on domains or instruments, but common themes:<sup>4,5</sup>

1. Personal resources: education, income, wealth, housing
2. Mental state: **mental health**, locus of control, purpose
3. Social connection: marital status, children, social participation

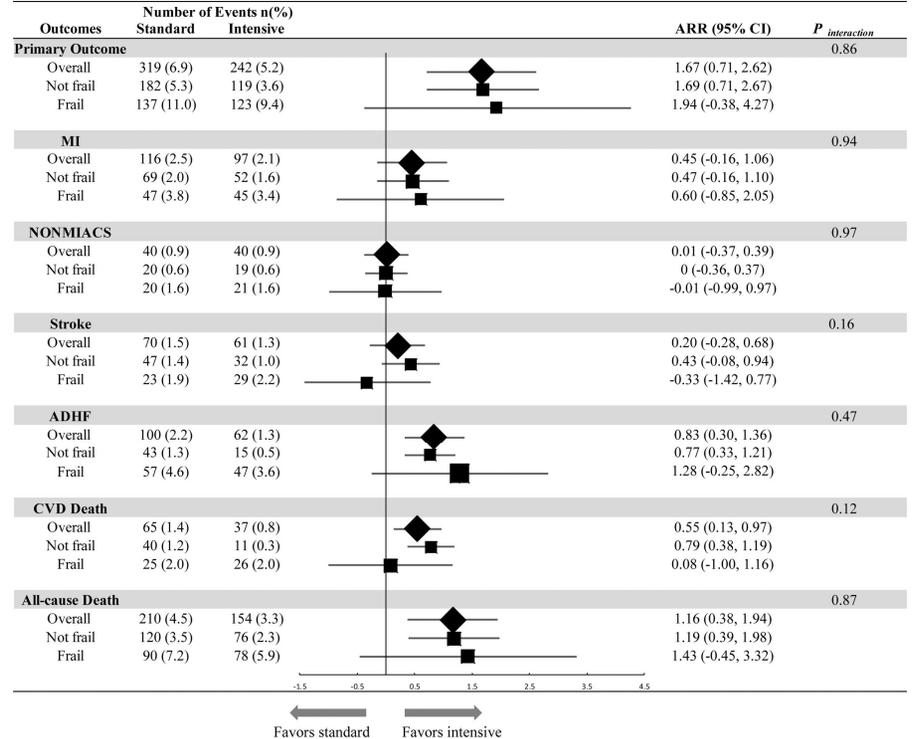
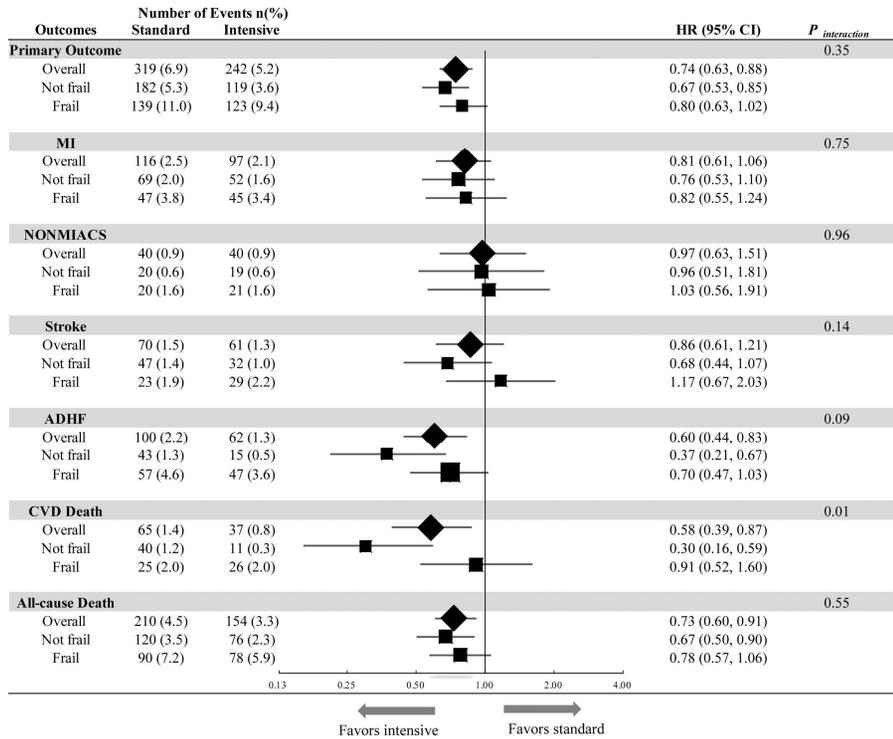


1. Shah SJ, et al. *PNAS*. 2023;120(7):e2209414120.
2. Li X, et al. *Aging Clin Exp Res*. 2023;35(7):1417-1428.
3. Goto T, et al. *Sci Rep*. 2024;14(1):3410.
4. Bunt S, et al. *Eur J Ageing*. 2017;14(3):323-334.
5. Montayre J, et al. *Gerontologist*. 2024;64(10):gnae114.

# Does Frailty Have Decision-Making Value?



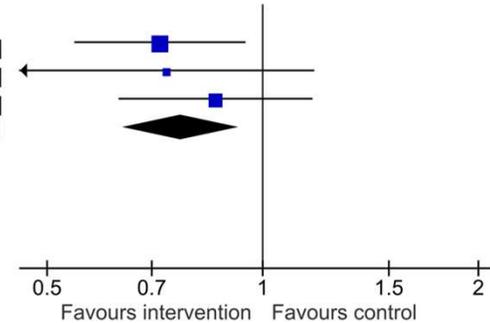
Varley PR, Buchanan D, Bilderback A, et al. *JAMA Surg.* 2023;158(5):475-483.



Wang Z, Du X, Hua C, et al. *Circulation*. 2023;148(7):565-574.

- The evidence is strongest for comprehensive geriatric assessment<sup>1</sup>

CGA						
Mazya et al. 2018	54	135	54	97	47.4%	0.72 [0.55, 0.94]
Li et al. 2010	23	129	34	140	15.8%	0.73 [0.46, 1.18]
Behm et al. 2016	58	171	45	114	36.8%	0.86 [0.63, 1.17]
<b>Subtotal (95% CI)</b>		<b>435</b>		<b>351</b>	<b>100.0%</b>	<b>0.77 [0.64, 0.93]</b>
Total events	135		133			
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.77, df = 2 (P = 0.68); I <sup>2</sup> = 0%						
Test for overall effect: Z = 2.73 (P = 0.006)						



- Low-strength evidence for physical activity & nutritional interventions<sup>2</sup>

- Macdonald SH, Travers J, Shé ÉN, et al. *PLoS One*. 2020;15(2):e0228821.
- Kim DH, Rockwood K. *N Engl J Med*. 2024;391(6):538-548.

### Management is multi-component:<sup>1,2,3</sup>

- Exercise
  - Resistance training
  - Group exercise
- Nutrition
  - Weight loss
  - Protein-calorie
  - Micronutrients
- Polypharmacy/Deprescribing

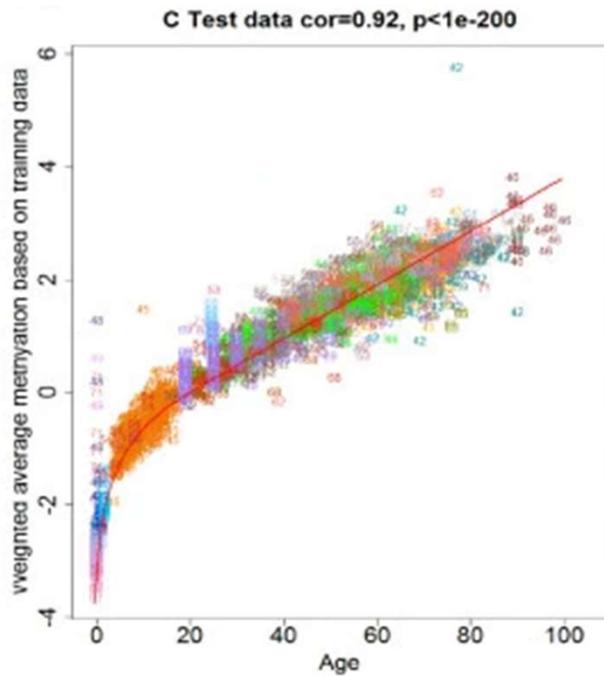
1. Dent E, et al. *J Nutr Health Aging*. 2019;23(9):771-787.
2. Apóstolo J, et al. *JBI Database System Rev Implement Rep*. 2018;16(1):140-232.
3. Kim DH, Rockwood K. *N Engl J Med*. 2024;391(6):538-548.

# Managing Frailty

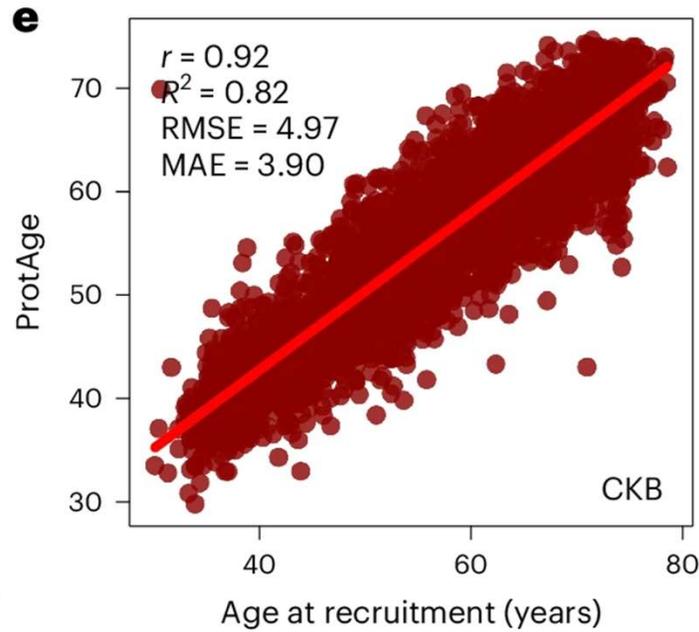
	Fit	Prefrailty	Frailty	End-Stage Frailty
<b>Frailty Score</b>	Fried frailty phenotype, 0 points Deficit-accumulation frailty index of <0.10 Score on Clinical Frailty Scale, 1-3	Fried frailty phenotype, 1 or 2 points Deficit-accumulation frailty index of 0.10 to <0.20 Score on Clinical Frailty Scale, 4	Fried frailty phenotype, 3 or 4 points Deficit-accumulation frailty index of 0.20 to <0.55 Score on Clinical Frailty Scale, 5-7	Fried frailty phenotype, 5 points Deficit-accumulation frailty index of ≥0.55 Score on Clinical Frailty Scale, 8 or 9
<b>Goal</b>	Increase physiological reserve	Increase physiological reserve	Preserve physiological reserve and prevent avoidable stressors	Provide comfort
<b>Lifestyle</b>	Exercise and physical activity High-quality diet Social engagement	Exercise and physical activity High-quality diet (protein intake) Social engagement	Less intense exercise may be better tolerated High-quality diet (protein intake) Social engagement	Physical activity as tolerated Diet as tolerated Social engagement as tolerated
<b>Disease Management</b>	Apply disease-based guidelines	Apply disease-based guidelines	Consider trade-off between disease and treatment burden	Deescalate treatments
<b>Preventive Care</b>	Vaccination Cancer screening	Vaccination Cancer screening	Vaccination Individualize cancer screening (time to benefit vs. remaining life expectancy)	Vaccination Stop cancer screening
<b>Interventions for Frailty</b>		Treat reversible causes of frailty Exercise and physical activity Nutritional counseling and supplementation CGA and multidisciplinary intervention Comprehensive medication review	Treat reversible causes of frailty Rehabilitation (PT and OT) Nutritional counseling and supplementation CGA and multidisciplinary intervention Comprehensive medication review	Comprehensive medication review
<b>Patient Engagement</b>	Patient-centered goal	Patient-centered goal	Patient-centered goal	Patient-centered goal
<b>Social Support</b>	Social support (family and caregiver)	Social support (family and caregiver)	Social support (family and caregiver)	Social support (family and caregiver)

# Related Ideas: Biological Age and Intrinsic Capacity

# Biological Age Measures



Horvath S. *Genome Biol.* 2013;14(10):R115.

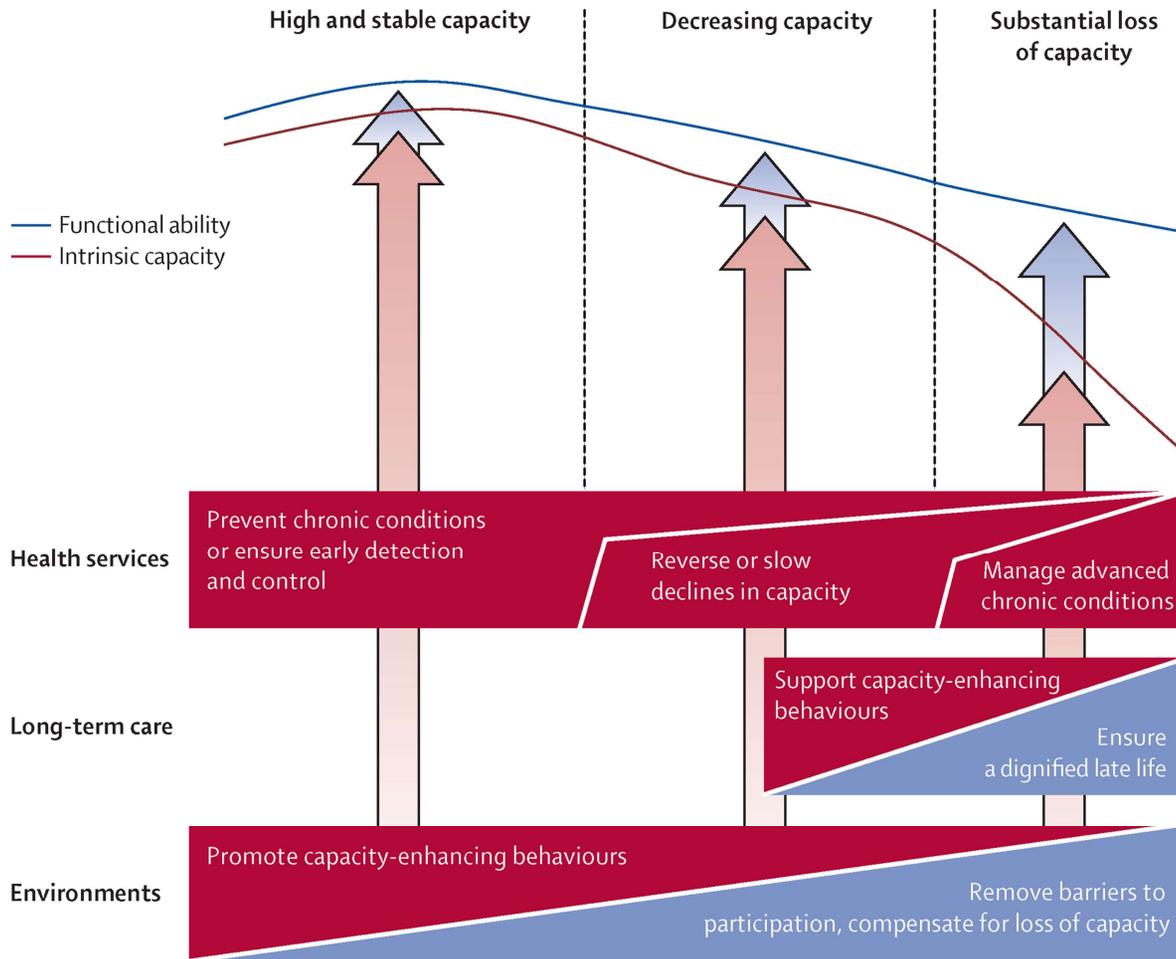


Argentieri MA, Xiao S, Bennett D, et al. *Nat Med.* 2024;30(9):2450-2460



Bontempi D, Zalay O, Bitterman DS, et al. *Lancet Digit Health.* 2025;7(6):100870.

# Intrinsic Capacity



Beard *et al. Lancet* 2016; 387(10033): 2145-2154.  
WHO. *World Report on Ageing and Health*. 2015.

**Table 3.1**  
Basic assessment for loss of intrinsic capacity

	Filter question If YES, proceed for in-depth assessment (Step 2)	Tests	Assess fully any domain with a checked circle	Pass
<b>5</b> Cognitive decline (Cognition)	Do you have problems with memory or orientation (such as not knowing where you are or what day it is)?	<ol style="list-style-type: none"> <li><b>Remember three words</b> (use nouns, for example): flower, door, rice.</li> <li><b>Orientation in time and space:</b> What is the full date today? Where are you now (home, clinic, etc.)?</li> <li>Recalls the three words?</li> </ol>	<input type="radio"/> Wrong to <b>either</b> question or does not know  <input type="radio"/> Cannot recall all three words	<input type="radio"/> Correct to <b>both</b> questions
<b>6</b> Limited mobility (Locomotor capacity)		<b>Chair rise test</b> Rise from chair five times without using arms. Did the person complete five chair rises within 14 seconds?	<input type="radio"/> No	<input type="radio"/> Yes
<b>7</b> Undernutrition (Vitality)		<ol style="list-style-type: none"> <li><b>Weight loss</b> Have you unintentionally lost more than 3 kg over the last 3 months?</li> <li><b>Appetite loss</b> Have you experienced loss of appetite?</li> </ol>	<input type="radio"/> Yes  <input type="radio"/> Yes	<input type="radio"/> No to <b>both</b> questions
<b>8</b> Vision impairment (Vision)	Do you have any problems with your eyes: difficulties in seeing far or near*, eye pain or discomfort?  Do you have diabetes, or hypertension, or are currently using steroids or eye medications?  <small>*with spectacles if normally worn</small>	<ol style="list-style-type: none"> <li><b>External eye check</b></li> <li><b>Visual acuity test</b> using WHO vision screening chart*:               <ul style="list-style-type: none"> <li>Distance vision (6/12 for each eye)</li> <li>Near vision (N6 for both eyes)</li> </ul> </li> </ol>	<input type="radio"/> Fail  <input type="radio"/> Fail	<input type="radio"/> Pass  <input type="radio"/> Pass for <b>both</b> distance and near vision
<b>9</b> Hearing loss (Hearing)	Do you have a hearing problem? <small>For those using a hearing aid(s) add, "even when using your hearing aid(s)".</small>	<b>Whisper test</b> or <b>Screening audiometry</b> or <b>Digits-triplet-in-noise test</b>	<input type="radio"/> Fail	<input type="radio"/> Pass
<b>10</b> Depressive symptoms (Psychological capacity)		<b>Over the past 2 weeks, have you been bothered by either of the following:</b> <ul style="list-style-type: none"> <li>Feeling down, depressed or hopeless?</li> <li>Little interest or pleasure in doing things?</li> </ul>	<input type="radio"/> Yes  <input type="radio"/> Yes	<input type="radio"/> No to <b>both</b> questions

WHO. *Integrated care for older people (ICOPE)*. 2E. 2024.

# WHO ICOPE Handbook App

Universal Projects & Tools, SL

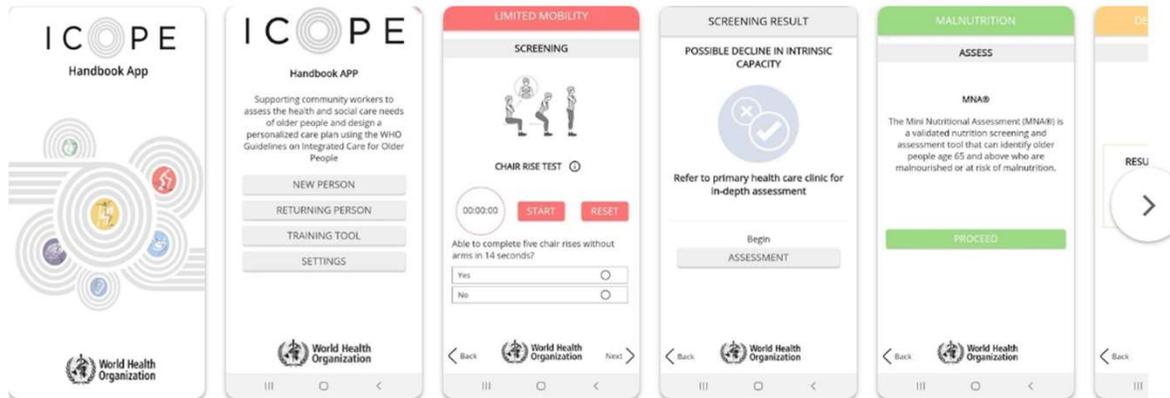
10K+  
Downloads

 Everyone

Install on more devices

 Share

 This app is available for your device



# Gaps and Opportunities

- New Techniques/Data
  - Machine learning
  - Unstructured EHR data
- Linking frailty and aging biology
  - Establishing causal links with biology of aging
  - Phenotypes of frailty rooted in aging biology
- Replace current frailty definitions with those rooted in aging biology?

- Implementing frailty in health systems
  - Remote assessments of frailty
  - Electronic frailty indices
  - Frailty screening by non-geriatricians
  - Comprehensive Geriatric Assessment
- Calibrating frailty assessments to risk
  - Mortality
  - Hospitalization
  - Institutionalization
  - Functional Independence

- High-Stress Settings:

Implementation	What to do?
Surgery	Solid Organ Transplantation
Oncology	Hospital Medicine
Cardiology	Intensive Care

- Low-Stress Settings:

- Frailty and treatment targets: hypertension, diabetes, heart failure
- Frailty and cancer screening

- Treating frailty

- Cost-Effectiveness

1. Frailty is the most prominent of many efforts to measure aging
2. What frailty does well
  - Research phenotype of aging
  - Risk-stratification of older adults
  - Decision-making before very stressful events (e.g. surgery)
3. Where we need more data
  - Harmonizing frailty assessment & tying it to physiology
  - Frailty and less-stressful events (e.g. starting a new medication)
  - How to manage frailty itself

- VA Career Development Award IK2CX002648
- National Institute on Aging R03AG082989
- CDA Mentors
  - David Ganz
  - Matthew Goetz
  - David Beenhouwer
  - Onyebuchi Arah
- Ariela Orkaby

Thank you

<https://www.duke-nus.edu.sg/care/>