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PHYSICAL FRAILTY & SARCOPENIA AS A NEW TARGET FOR INTERVENTIONS

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Roma

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From the Disease-Centered Paradigm to a Holistic Approach for the Care of Older People

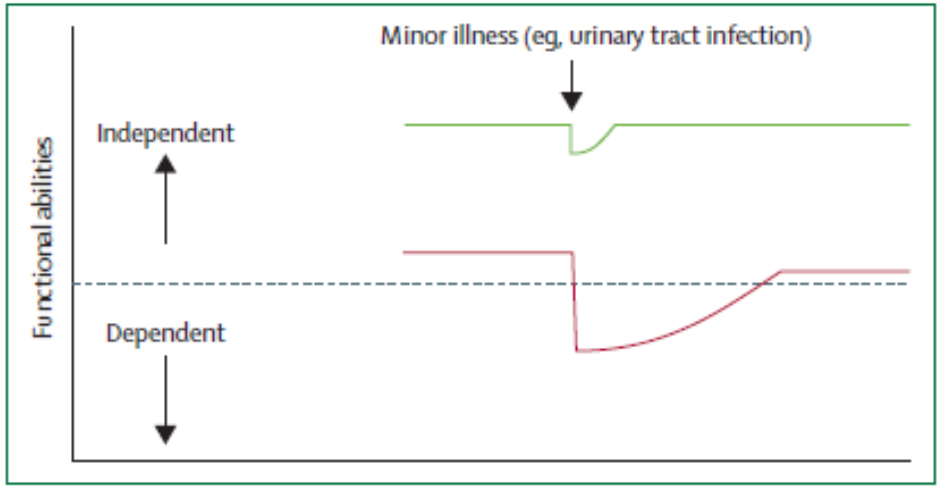
- Healthcare systems are increasingly faced with a growing population of older adults characterized by the co-existence of multiple, chronic disabling conditions.
- The gap between the demand of effective intervention strategies and the availability of medical programs specifically dedicated to older adults results in inappropriate use of resources and escalating healthcare expenditures.
- The geriatric syndromes of frailty and sarcopenia have gained special interest due to their association with a number of potentially preventable adverse health outcomes.

Frailty in elderly people

THE LANCET

Andrew Clegg, John Young, Steve Iliffe, Marcel Olde Rikkert, Kenneth Rockwood

(..) a state of vulnerability to poor resolution of homeostasis following a stress and is a consequence of cumulative decline in multiple physiological systems over a lifespan. This cumulative decline erodes homeostatic reserve until relatively minor stressor events trigger disproportionate changes in health status (…)



Lancet 2013; 381: 752–62

THE ASSESSMENT OF FRAILTY: TYING UP LOOSE ENDS

- More than 40 operational definitions of frailty have been proposed in the literature (and the number is still increasing).
- Each instrument has a certain capacity of predicting negative outcomes in older people.

BUT

Each tool identifies a specific population at risk of negative outcomes, and the agreement of results across instruments is modest (at best).

Operationalization of Frailty Using Eight Commonly Used Scales and Comparison of Their Ability to Predict All-Cause Mortality

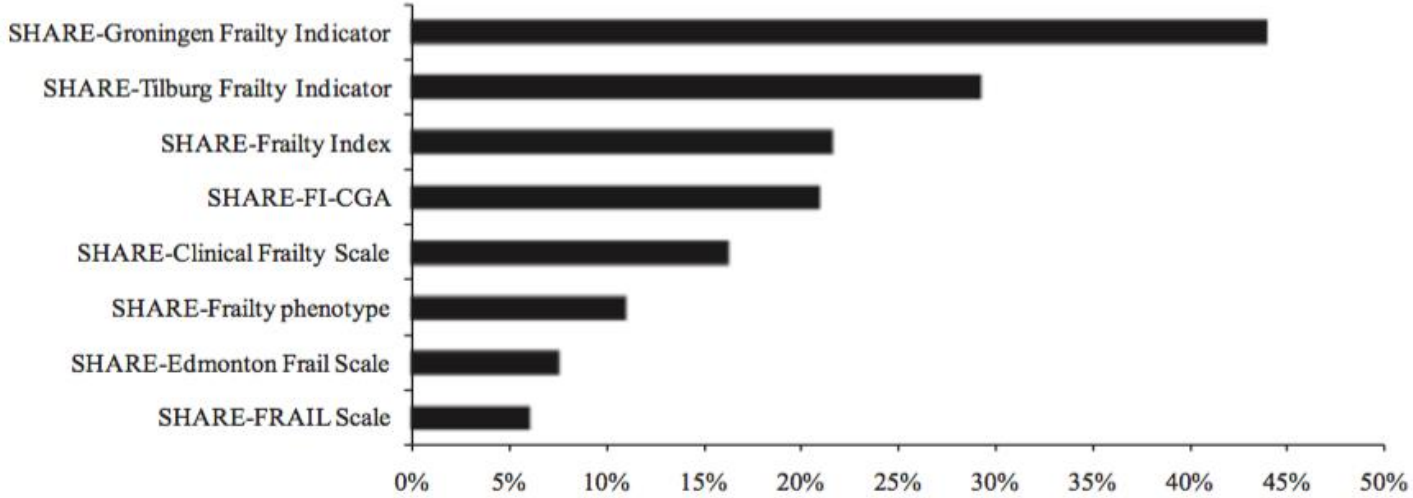


Figure 1. Prevalence of frailty. SHARE = Survey of Health, Ageing and Retirement in Europe; FI-CGA = Frailty Index based on a Comprehensive Geriatric Assessment.

Theou et al., J Am Geriatr Soc 2013

Synoptic view of diagnostic criteria of the most popular definitions of sarcopenia in alphabetic order

	Operationalization
European Working Group on Sarcopenia in Older People 2	Low muscle strength (grip strength <27 kg in men and <16 kg in women) plus low muscle mass (technique-specific cut-points)
FNIH Sarcopenia Project	Low muscle mass (ALM < 19.75kg in men and <15.02 kg in women, or ALM_{BMI} <0.789 in men and <0.512 in women) plus low muscle strength (handgrip strength <26 kg in men and <16 kg in women)
International Working Group on Sarcopenia	Low ALM/height^2 (≤7.23 kg/m^2 in men and ≤5.67 kg/m^2 in women) plus low physical function (gait speed <1.0 m/s)
Sarcopenia with limited mobility	Low physical function (gait speed ≤1.0 m/s or <400 meters walked during 6 min) plus low appendicular lean mass (≥2 standard deviations below the mean measured in healthy persons aged 20-30 years old from the same ethnic group)
Special Interest Group: cachexia-anorexia in chronic wasting diseases	Low muscle mass (≥2 SDs below the mean measured in young adults of the same sex and ethnic background) plus low physical function (gait speed <0.8 m/s)

Who has sarcopenia?

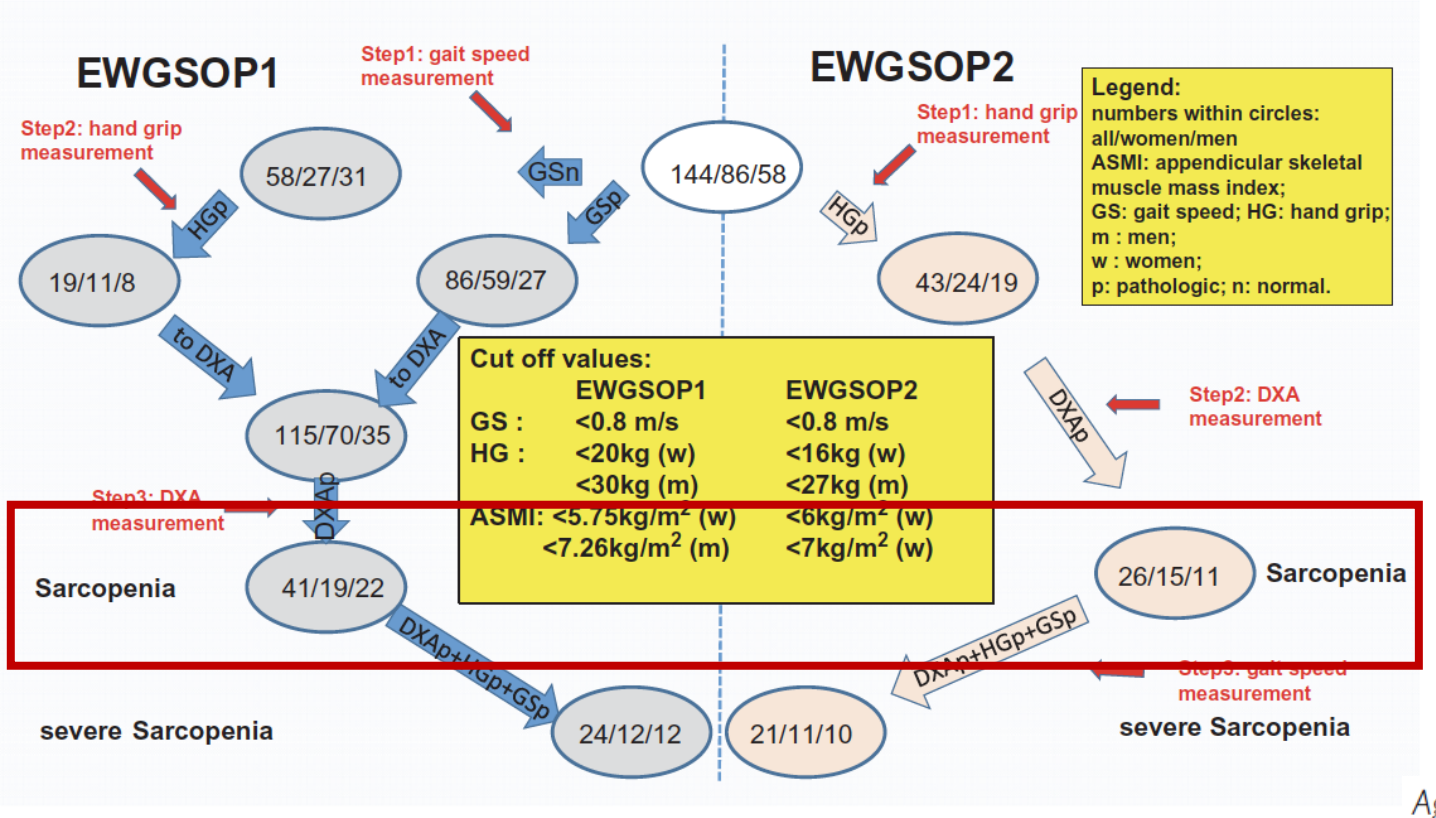
Table 1. Summary of Operational Definitions for Sarcopenia and Prevalence by Gender

Criteria	Operational Definition: Physical Performance	Operational Definition: Muscle Strength	Operational Definition: ALM	Prevalence (%): Men (n = 7,113)	Prevalence (%): Women (n = 2,950)
Foundation of NIH Sarcopenia Project					
Weakness and low lean mass	—	Grip strength Men: <26 kg Women: <16 kg	ALM_{BMI} Men: <0.789 Women: <0.512	1.3	2.3
Slowness with weakness and low lean mass	Gait speed: ≤0.8 m/s	Grip strength Men: <26 kg Women: <16 kg	ALM_{BMI} Men: <0.789 Women: <0.512	0.5	1.8
International Working Group	Gait speed: <1.0 m/s	—	ALM/ht^2 Men: ≤7.23 kg/m² Women: ≤5.67 kg/m²	5.1	11.8
European Working Group on Sarcopenia Older Persons					
Sarcopenia	Gait speed: <0.8 m/s or Grip strength Men: <30 kg Women: <20 kg		ALM/ht^2 Men: ≤7.23 kg/m² Women: ≤5.67 kg/m²	5.3	13.3
Severe sarcopenia	Gait speed: <0.8 m/s	Grip strength Men: <30 kg Women: <20 kg	ALM/ht^2 Men: ≤7.23 kg/m² Women: ≤5.67 kg/m²	0.7	2.9

Note: ALM_{BMI} = ratio of appendicular lean mass over body mass index; ALM/ht^2 = ratio of appendicular lean mass over height squared.

Dam et al., J Gerontol A Biol Sci Med Sci 2014

Consequences of applying the new EWGSOP2 guideline instead of the former EWGSOP guideline for sarcopenia case finding in older patients

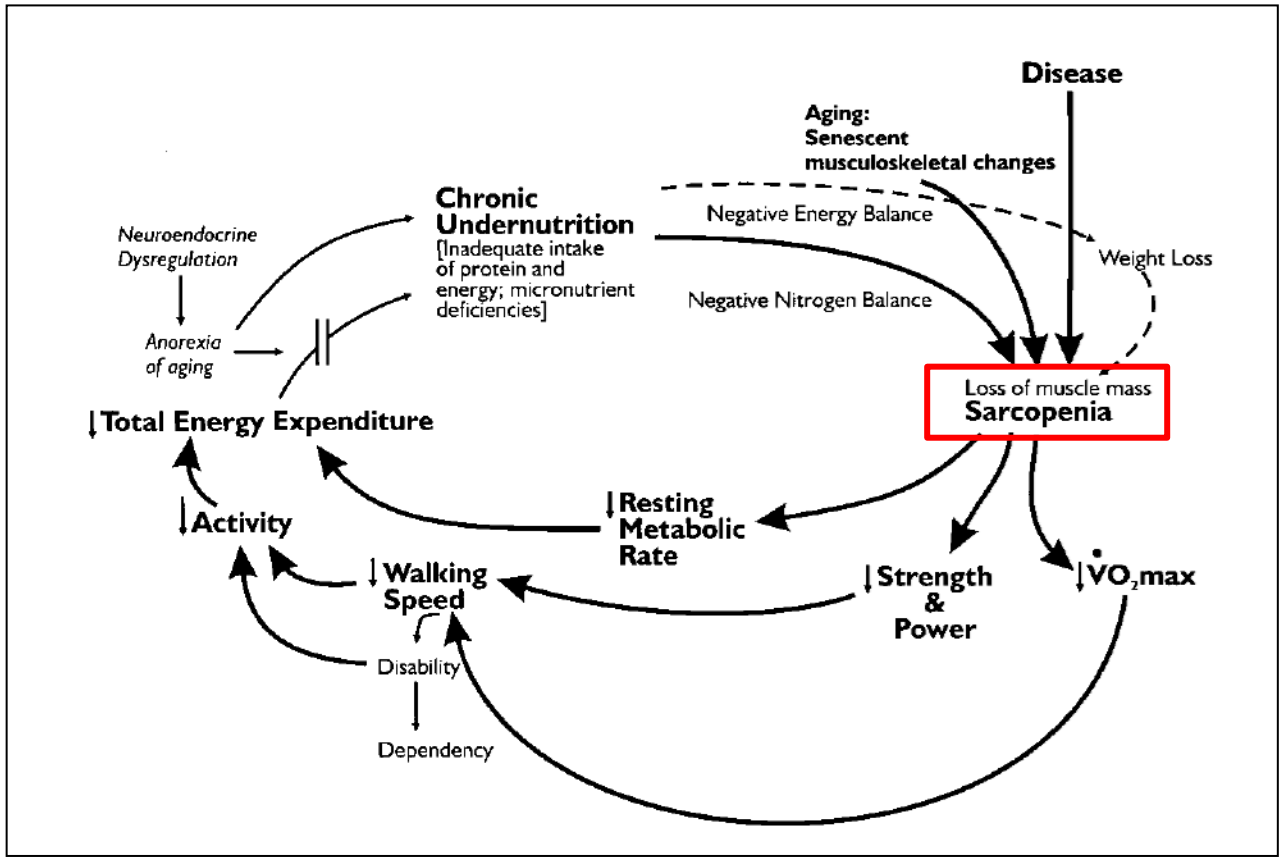


28.5%

18.1%

Age and Ageing 2019; **0:** 1–6
doi: 10.1093/ageing/afz035

THE FRAILTY PHENOTYPE AND SARCOPENIA



Fried et al., J Gerontol A Biol Sci Med Sci 2001

frontiers in
AGING NEUROSCIENCE

OPINION ARTICLE
published: 28 July 2014
doi: 10.3389/fnagi.2014.00192

Sarcopenia and physical frailty: two sides of the same coin

Matteo Cesari[1,2]*, *Francesco Landi*[3], *Bruno Vellas*[1,2], *Roberto Bernabei*[3] and *Emanuele Marzetti*[3]

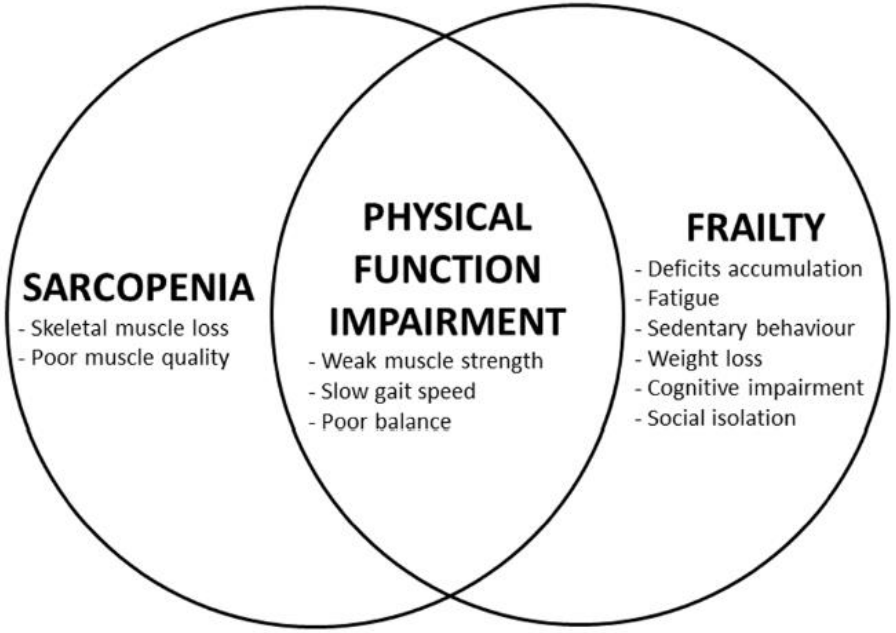


FIGURE 1 | Relationship among sarcopenia, frailty, and physical function impairment.

Clin Geriatr Med ■ (2015) ■–■
http://dx.doi.org/10.1016/j.cger.2015.04.005

Sarcopenia as the Biological Substrate of Physical Frailty

Francesco Landi, MD, PhD[a,*], Riccardo Calvani, PhD[a,1], Matteo Cesari, MD, PhD[b,1], Matteo Tosato, MD, PhD[a], Anna Maria Martone, MD[a], Roberto Bernabei, MD[a], Graziano Onder, MD, PhD[a], Emanuele Marzetti, MD, PhD[a]

PHYSICAL FRAILTY & SARCOPENIA: THE NEW KID ON THE BLOCK

Translational Medicine @ UniSa - ISSN 2239-9747

OPERATIONALIZATION OF THE PHYSICAL FRAILTY & SARCOPENIA SYNDROME: RATIONALE AND CLINICAL IMPLEMENTATION

E. Marzetti[1*§] , R. Calvani[2*] , M. Cesari[3,4] , M. Tosato[2] , A. Cherubini[5] , M. Di Bari[6] , M.Pahor[7] , G. Savera[2] , A. Collamati[2] , E. D'Angelo[2] , R. Bernabei[2] , F. Landi[2] ; on behalf of the SPRINTT Consortium

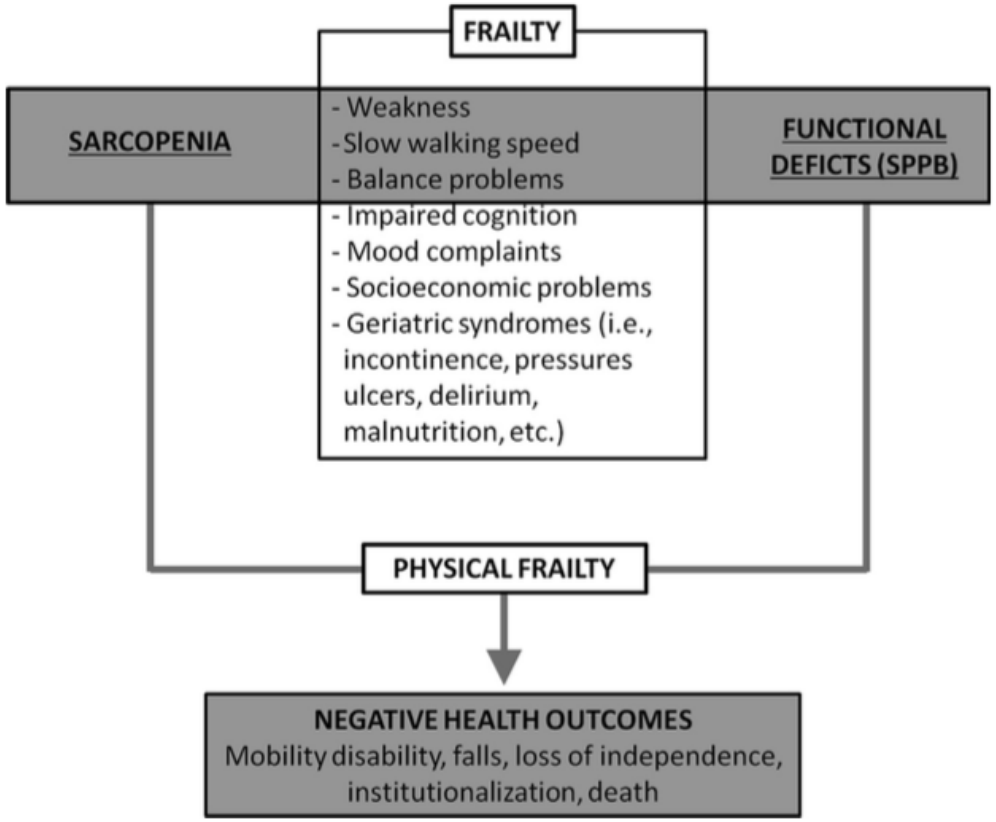
Sprintt CLINICAL TRIAL

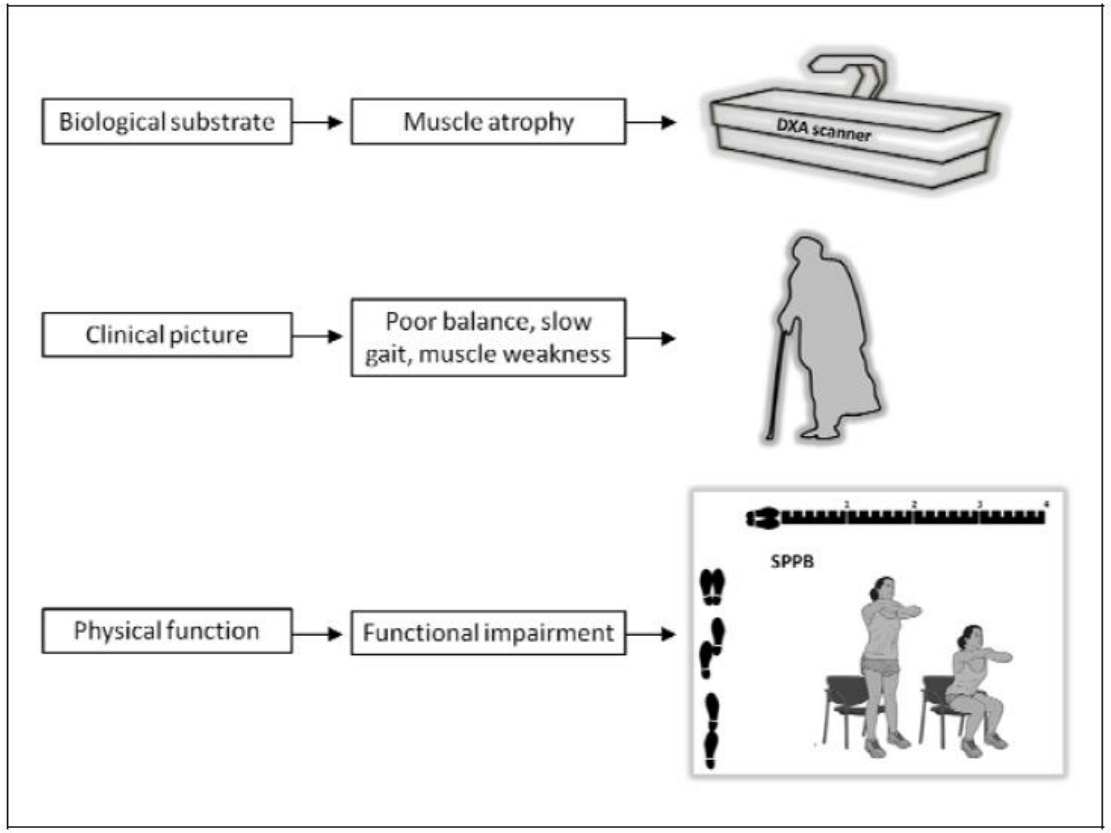
Frailty **B**ureau of **I**nvestigation

- ☐ 70+ year-old
- ☐ Underweight or overweight
- ☐ Uses a cane to get around and/or has a very slow pace
- ☐ Walks slowly and/or wobbly
- ☐ Needs help to rise from a chair
- ☐ Holds the handrails when walking up or down stairs

Marzetti et al., Exp Gerontol 2018

PHYSICAL FRAILTY AND SARCOPENIA: THE NEW KID ON THE BLOCK





Conceptual framework of physical frailty and sarcopenia—resemblance to common conditions of advanced age			
Condition	**Measurable Biological Substrate**	**Measurable Clinical Manifestations**	**Measurable Function**
CHF	Myocardial dysfunction (echocardiography)	• Shortness of breath • Fatigue	6-min walking test
COPD	Airways destructive changes (spirometry)	• Dyspnoea • Cough • Sputum	6-min walking test
PAD	Arterial stenosis (Doppler ultrasonography)	• Intermittent claudication • Numbness • Ulcers	Treadmill walking distance
PF&S	Reduced muscle mass (DXA)	• Slow walking speed • Poor balance • Weakness	SPPB

Landi et al., Clin Ger Med 2015

Journals of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 May;69(5):547–558
doi:10.1093/gerona/glu010

Special Article

The FNIH Sarcopenia Project: Rationale, Study Description, Conference Recommendations, and Final Estimates

Stephanie A. Studenski,[1] Katherine W. Peters,[2] Dawn E. Alley,[3] Peggy M. Cawthon,[2] Robert R. McLean,[4,5] Tamara B. Harris,[6] Luigi Ferrucci,[6] Jack M. Guralnik,[3] Maren S. Fragala,[7] Anne M. Kenny,[8] Douglas P. Kiel,[4,5] Stephen B. Kritchevsky,[9] Michelle D. Shardell,[3] Thuy-Tien L. Dam,[10] and Maria T. Vassileva[11]

Table 3. Recommendations for Cutpoints for Weakness and Low Lean Mass in Men and Women

Cutpoint	Men	Women
Weakness		
Recommended: grip strength (GSMAX)	<26 kg	<16 kg
Alternate: grip strength adjusted for BMI ($GSMAX_{BMI}$)	<1.0	<0.56
Appendicular lean body mass		
Recommended: ALM adjusted for BMI (ALM_{BMI})	<0.789	<0.512
Alternate: ALM	<19.75 kg	<15.02 kg

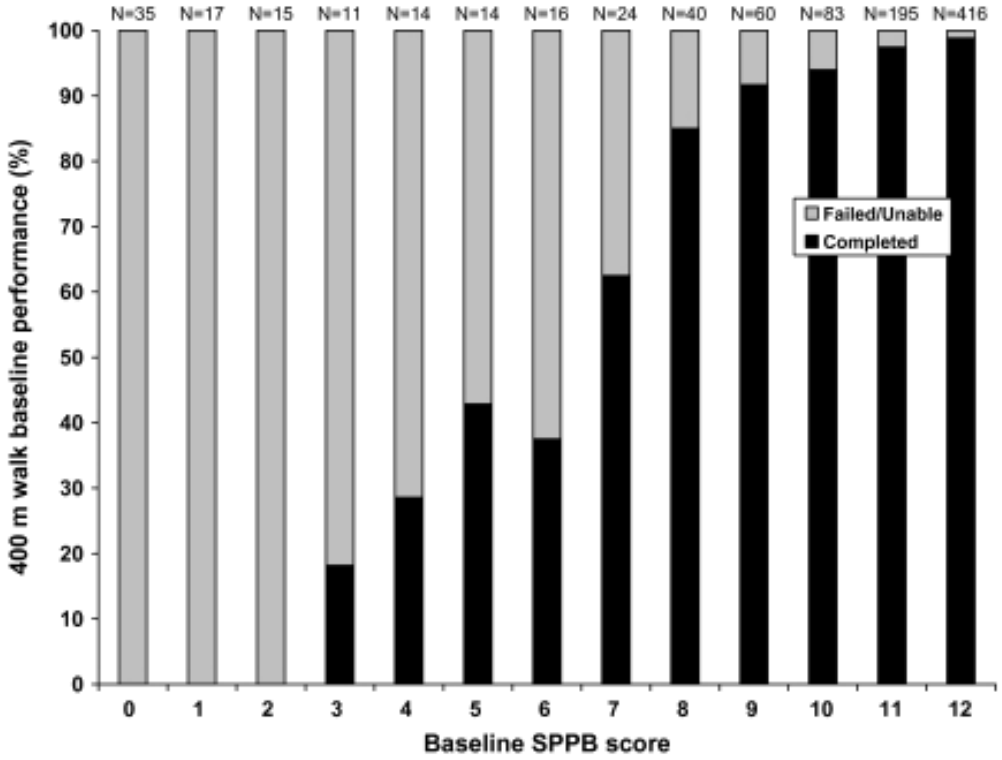
Notes: ALM = appendicular lean mass; BMI = body mass index.

Why Is the SPPB Fit-for-purpose?

- EMA indicated the SPPB as the preferred option to characterize physical frailty for intervention trials in older adults.
- The SPPB is increasingly used as an outcome measure in clinical trials in older adults (e.g., REHAB-HF).

SETTING THE SPPB RANGE

400-m walk baseline completion by SPPB score
Older people with SPPB <3 are unable to complete the test



Vasunilashorn et al., J Gerontol A Biol Sci Med Sci 2009

- Older adults scoring 10+ on the SPPB are commonly considered high-functioning (Guralnik et al., J Gerontol 1994)
- A cut-off of 9 in the SPPB has good sensitivity and specificity in discriminating frail from non-frail older adults (da Câmara et al., Geriat Gerontol Int 2013)
- Screening in primary care for non-disabled, older persons with SPPB ≤9 yields individuals with substantial morbidity, impairments, and functional limitations (Bandinelli et al., Aging Clin Exp Res. 2006)

Aging Clin Exp Res (2017) 29:81–88
DOI 10.1007/s40520-016-0716-1

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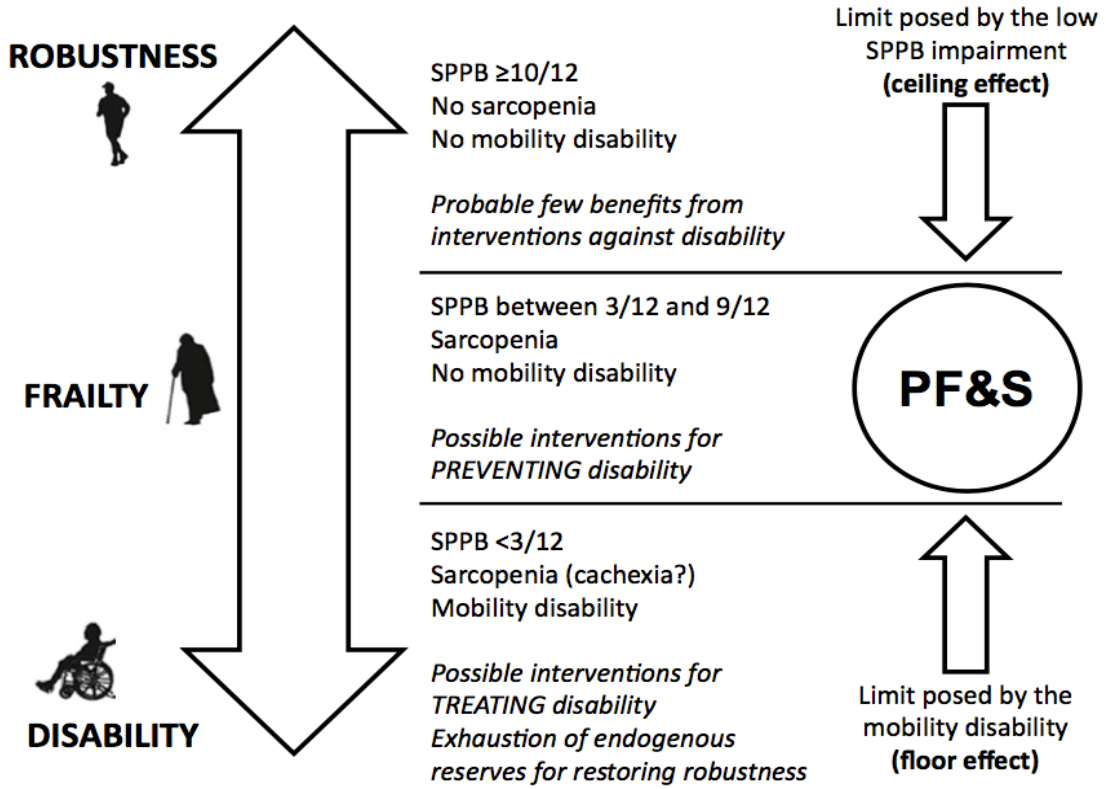
ORIGINAL ARTICLE

Rationale for a preliminary operational definition of physical frailty and sarcopenia in the SPRINTT trial

Matteo Cesari[1,2] · Francesco Landi[3] · Riccardo Calvani[3] · Antonio Cherubini[4] · Mauro Di Bari[5,6] · Patrick Kortebein[7,8,9] · Susanna Del Signore[10] · Regis Le Lain[11] · Bruno Vellas[1,2] · Marco Pahor[12] · Ronenn Roubenoff[13] · Roberto Bernabei[3] · Emanuele Marzetti[3] · For the SPRINTT Consortium



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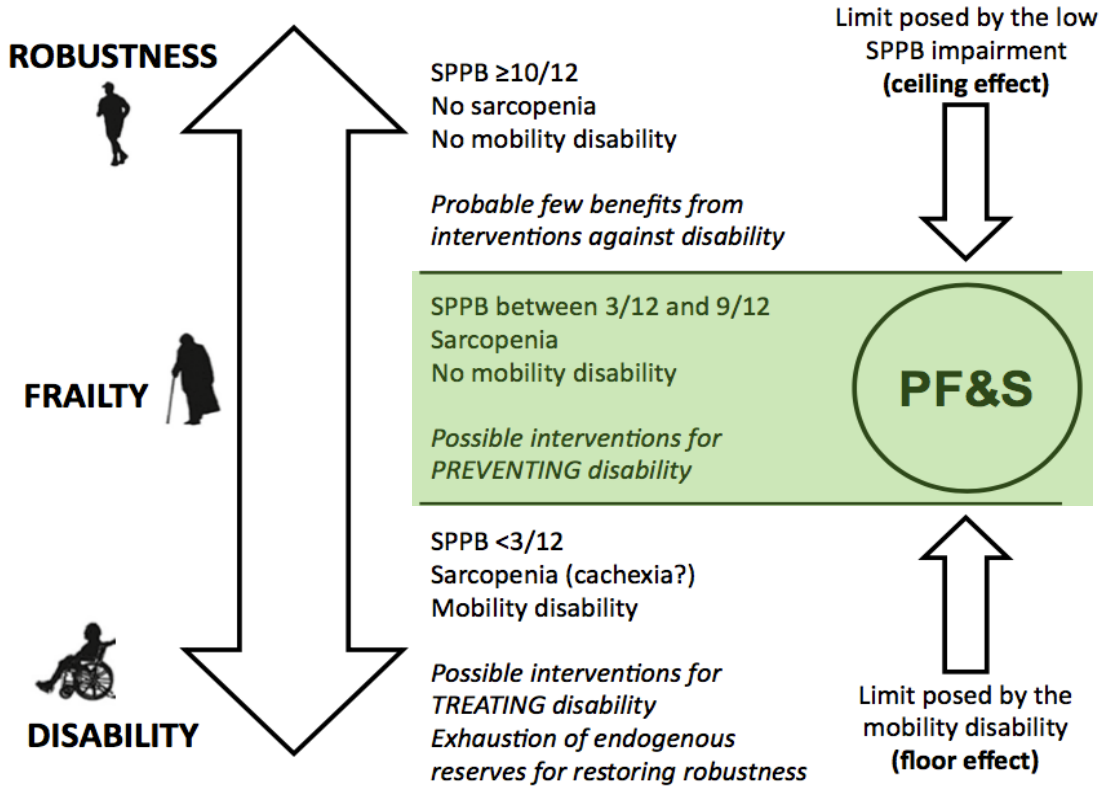

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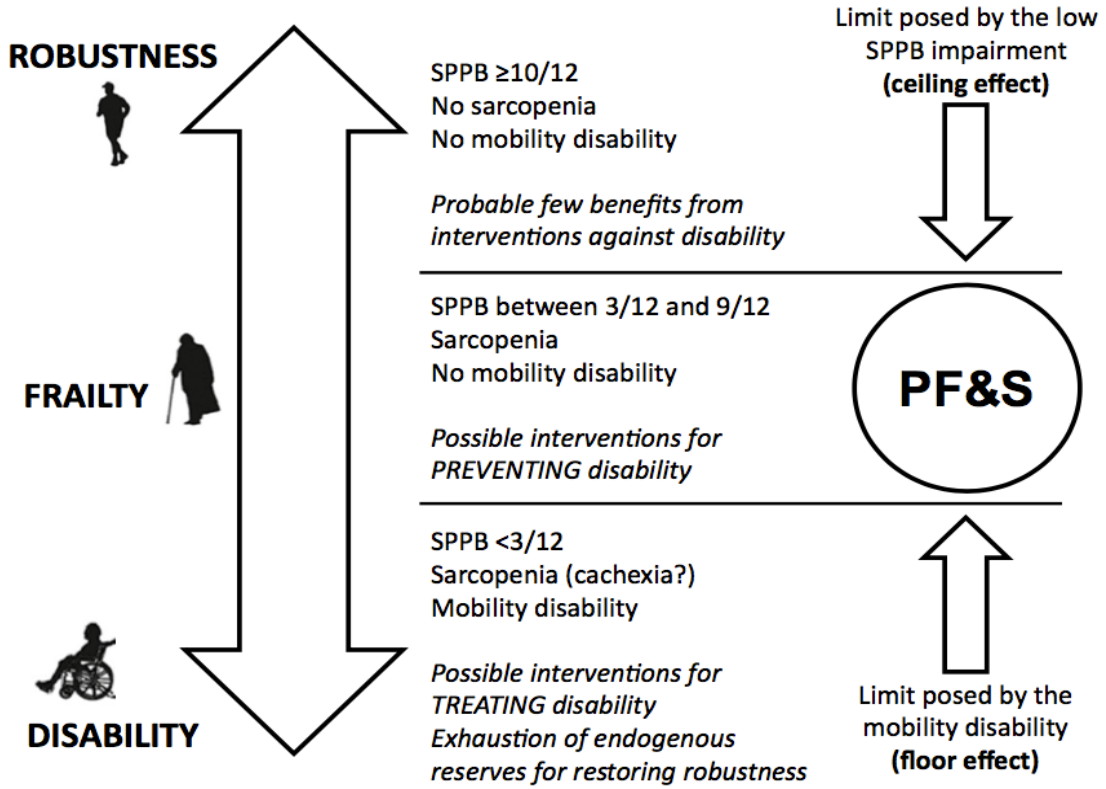

KEY POINTS

- The ongoing demographic transition is accompanied by substantial changes in medical needs, which imposes the development of counteractions against highly prevalent disabling conditions.
- The operationalization of PF&S surpasses the traditional medical paradigm of healing through treating a single disease by focusing on the functional domain.
- All of the components defining PF&S are objectively measurable, which facilitates its incorporation into standard practice.
- The recognition of a biological substratum of PF&S (i.e., skeletal muscle decline) opens new venues for the development of preventive and therapeutic interventions, including medicinal products.

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✓ **Innovative Medicines Initiative – Joint Undertaking (IMI–JU 115621)**
✓ Fondazione Roma (call for proposals NCDs 2013)

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