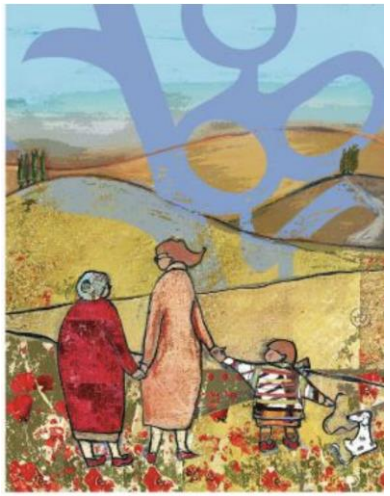


64° Congresso Società Italiana di Geriatria e Gerontologia
Auditorium della Tecnica
Roma - 28 Novembre 2019

Fenotipi della Fragilità

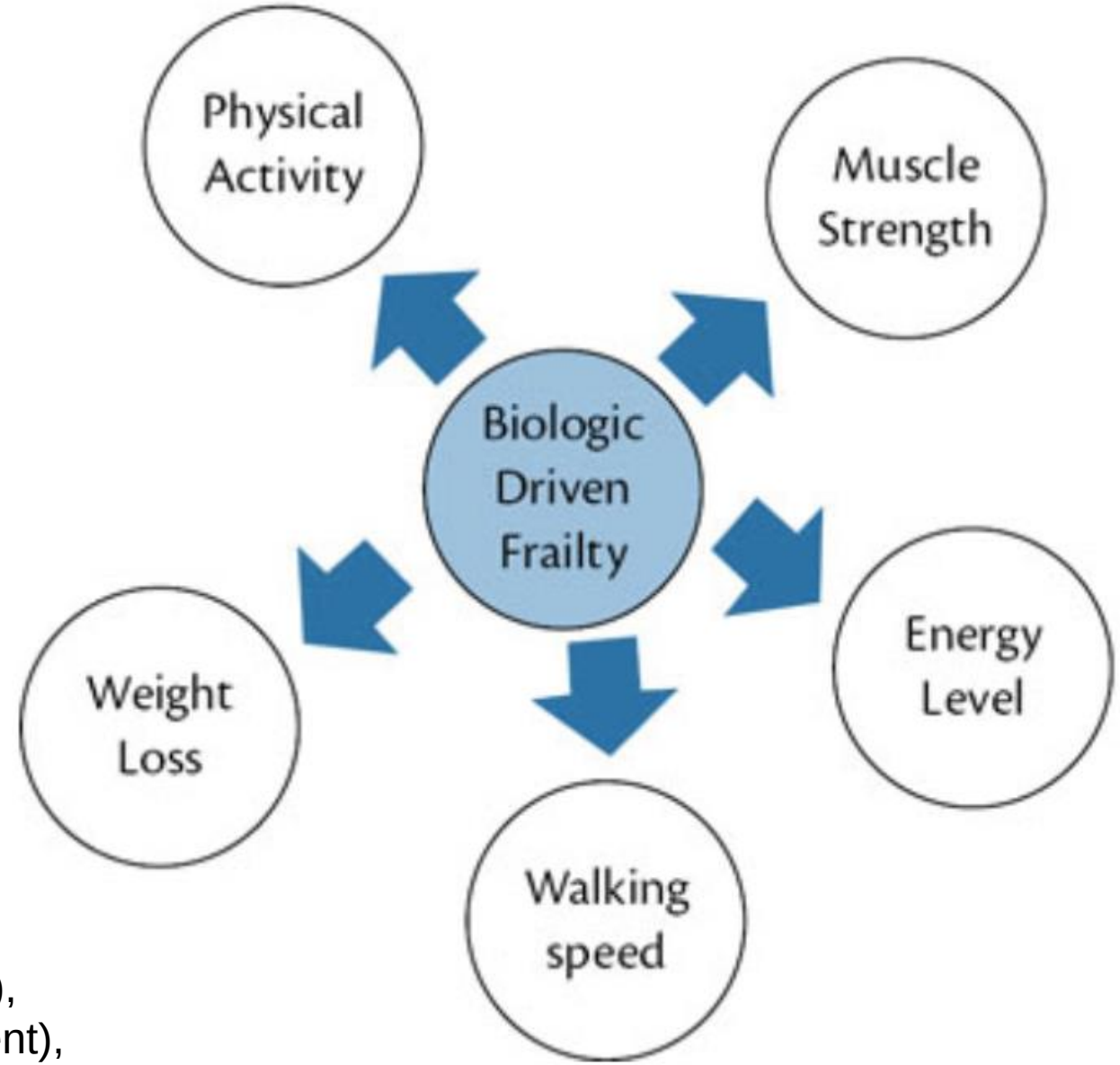
Fragilità Fisica

Vincenzo Solfrizzi

Università degli Studi di Bari, "A. Moro"
Centro per lo Studio dell'Invecchiamento cerebrale e le demenze
UO di Medicina Interna e Geriatria e Memory Unit

PHYSICAL FRAILTY: ONE OF THE MOST COMMON CONCEPTUALIZATIONS OF FRAILTY

Oxford Textbook of Geriatric Medicine
3° EDITION - 2018



Frailty states:
non-frail (0 criteria present),
pre-frail (1–2 criteria present),
frail (≥3 criteria present)

Fried L et al
J Gerontol (2001) 56A, M1-M11

Characteristics of physical frailty

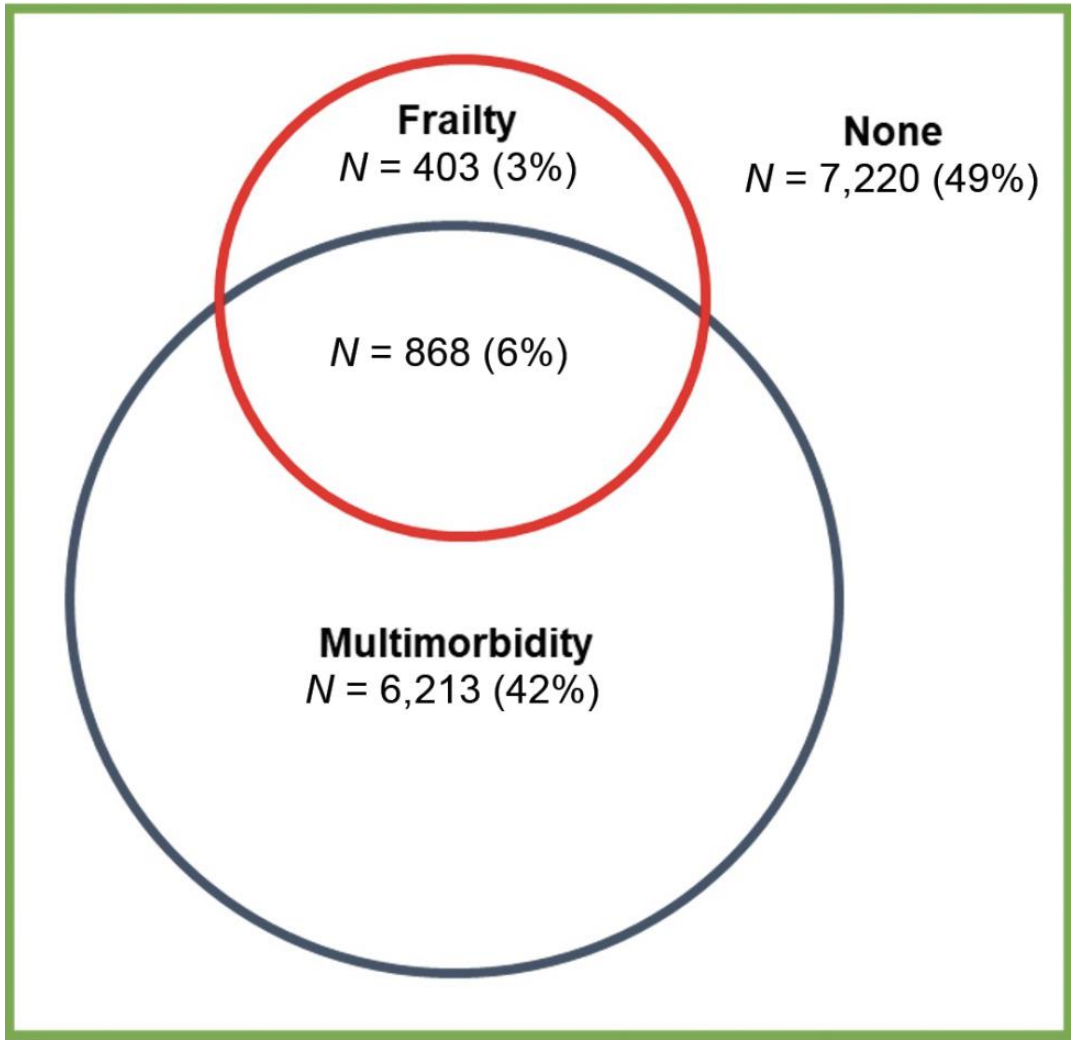
Frailty as a vulnerable health state is associated with an increased risk of a variety of adverse health outcomes.

Vulnerability has a dual meaning:

1) being an internal fragile health state with a lack of internal capacities and, at the same time,
2) being exposed to external harmful factors impinging on the person's capacities

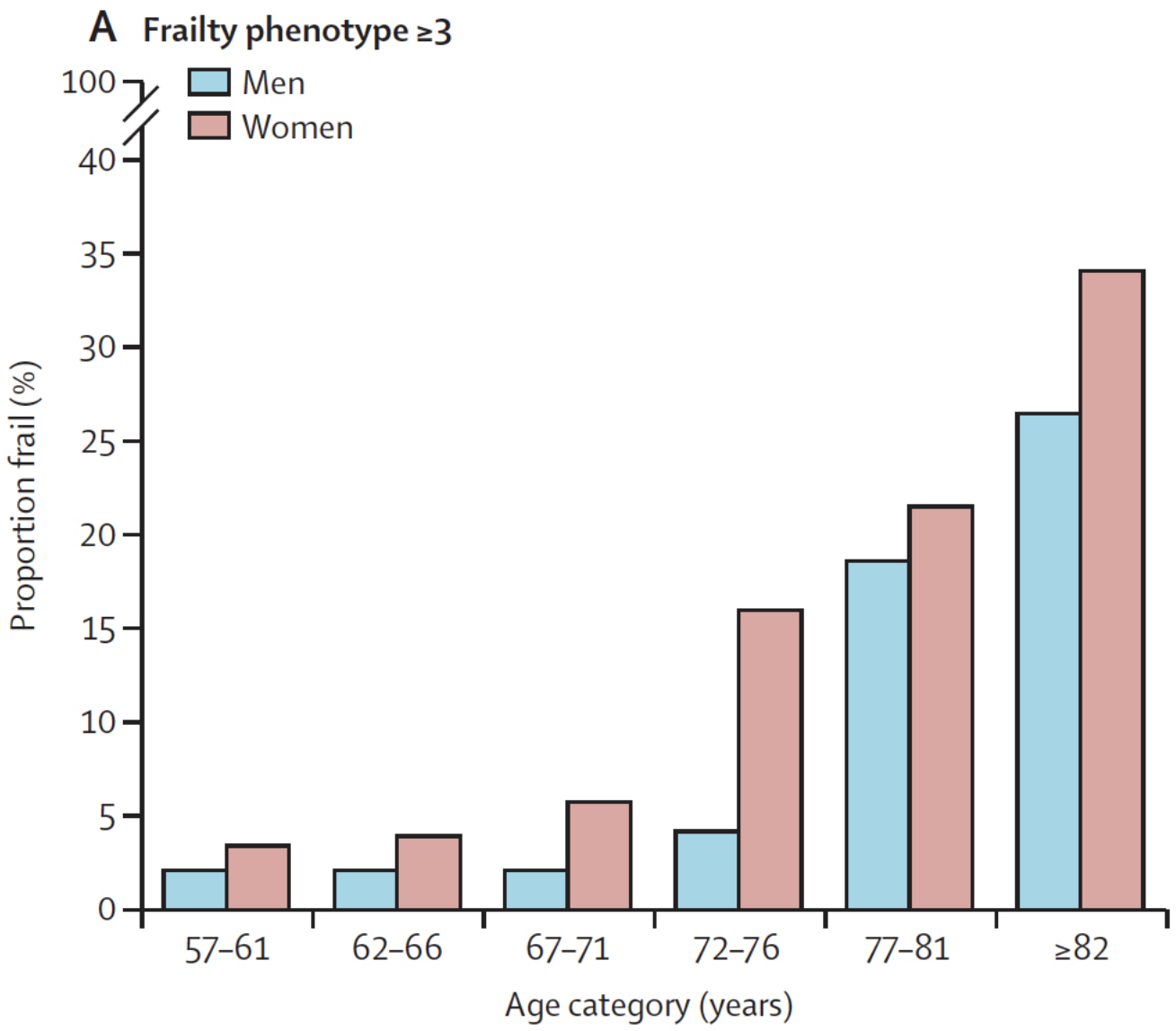
Junius-Walker U et al European Journal of Internal Medicine 56 (2018) 3–10

Overlap of frailty and multimorbidity



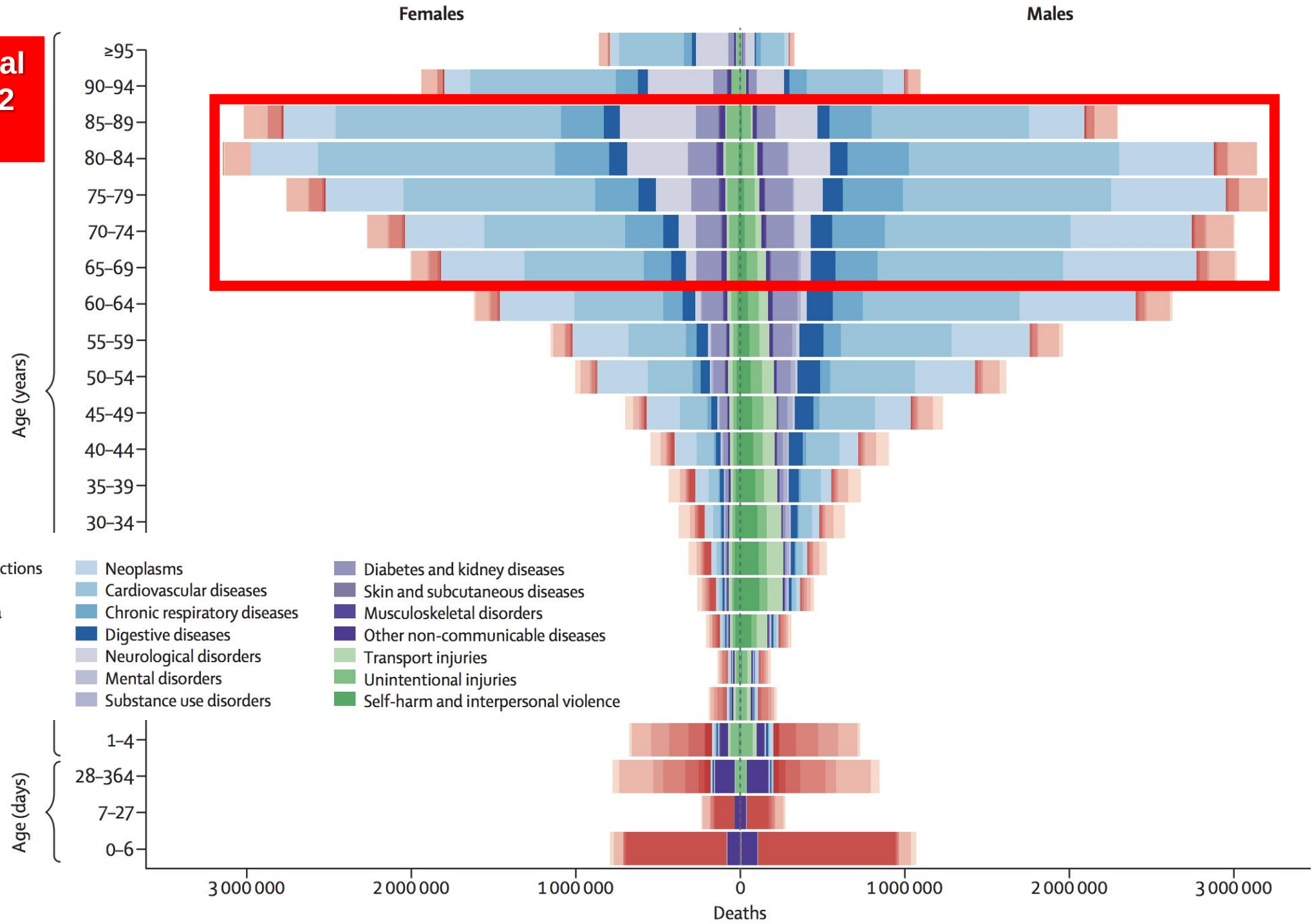
Vetrano DL et al J Gerontol A Biol Sci Med Sci, 2019, Vol. 74, No. 5, 659–666

Frailty prevalence for men and women by age



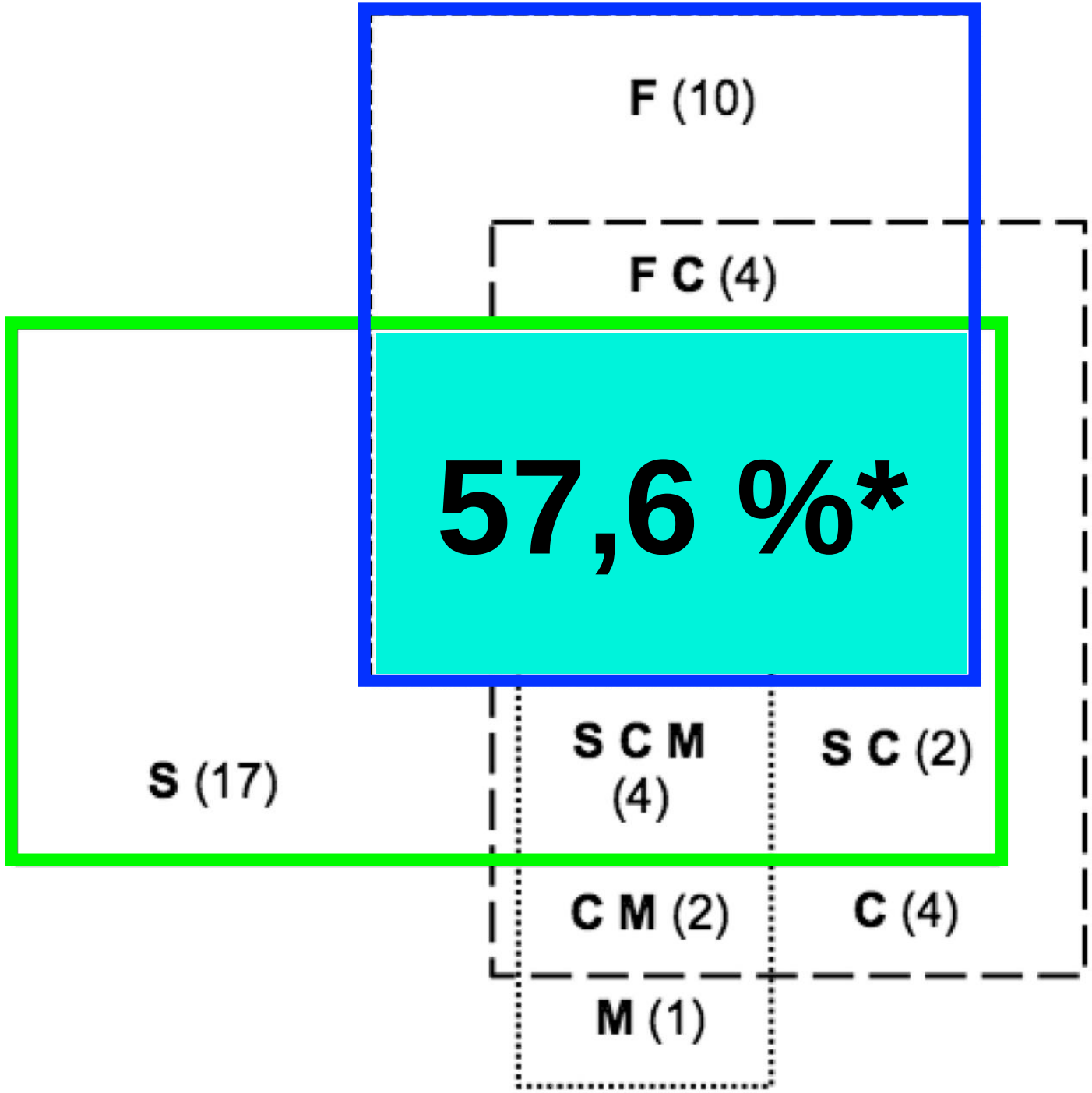
Hoogendijk EO, et al Eur J Epidemiol 2016; 31: 927–45

Sex difference in global mortality for 21 Level 2 causes by age, 2017



Lancet 2018; 392: 1736–88

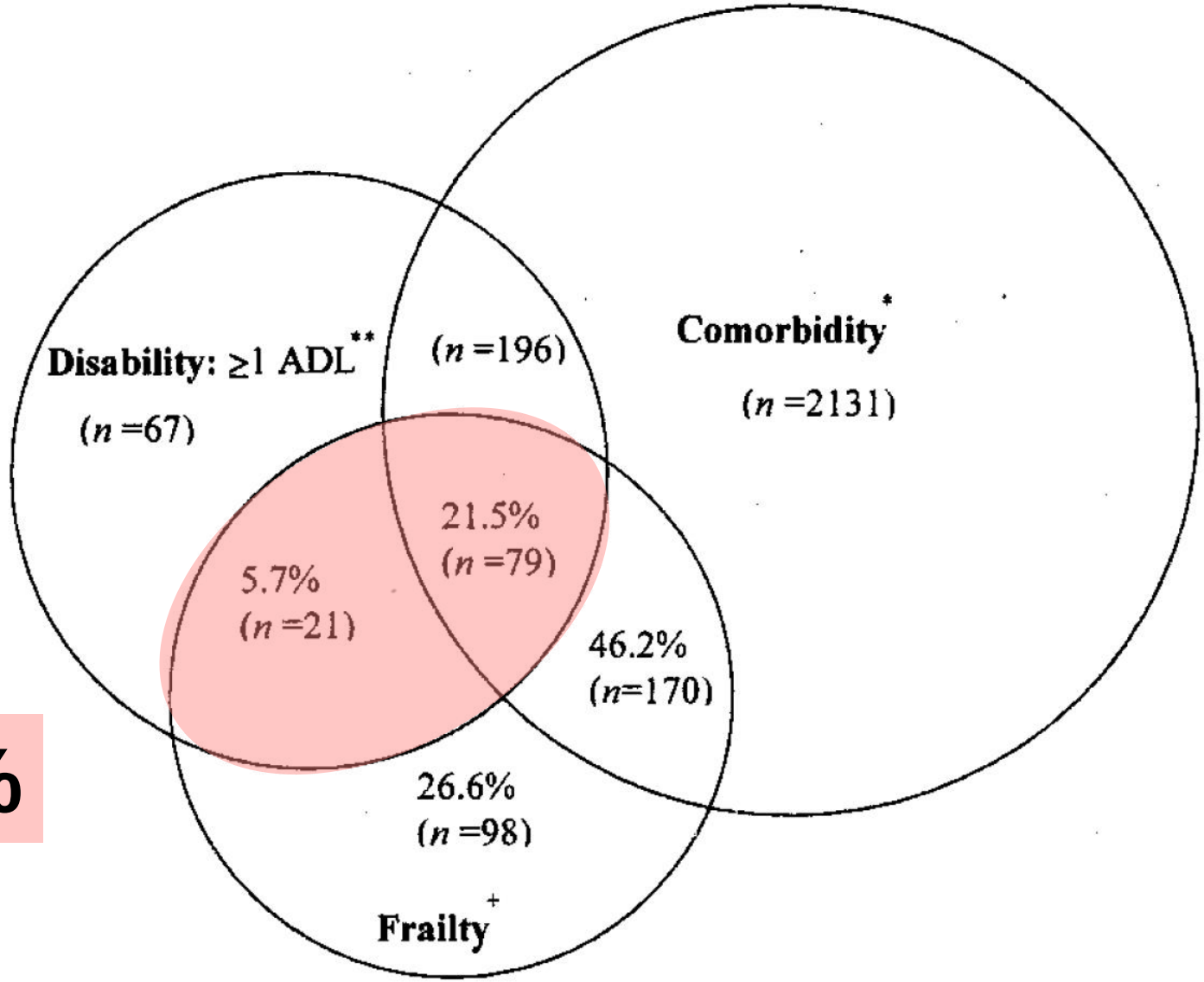
Overlap of sarcopenia (S), frailty (F), cachexia (C), and malnutrition (M) in older medical inpatients (n=100)



**Significant difference between patients with and patients without the respective syndrome ($p < 0.05$)*

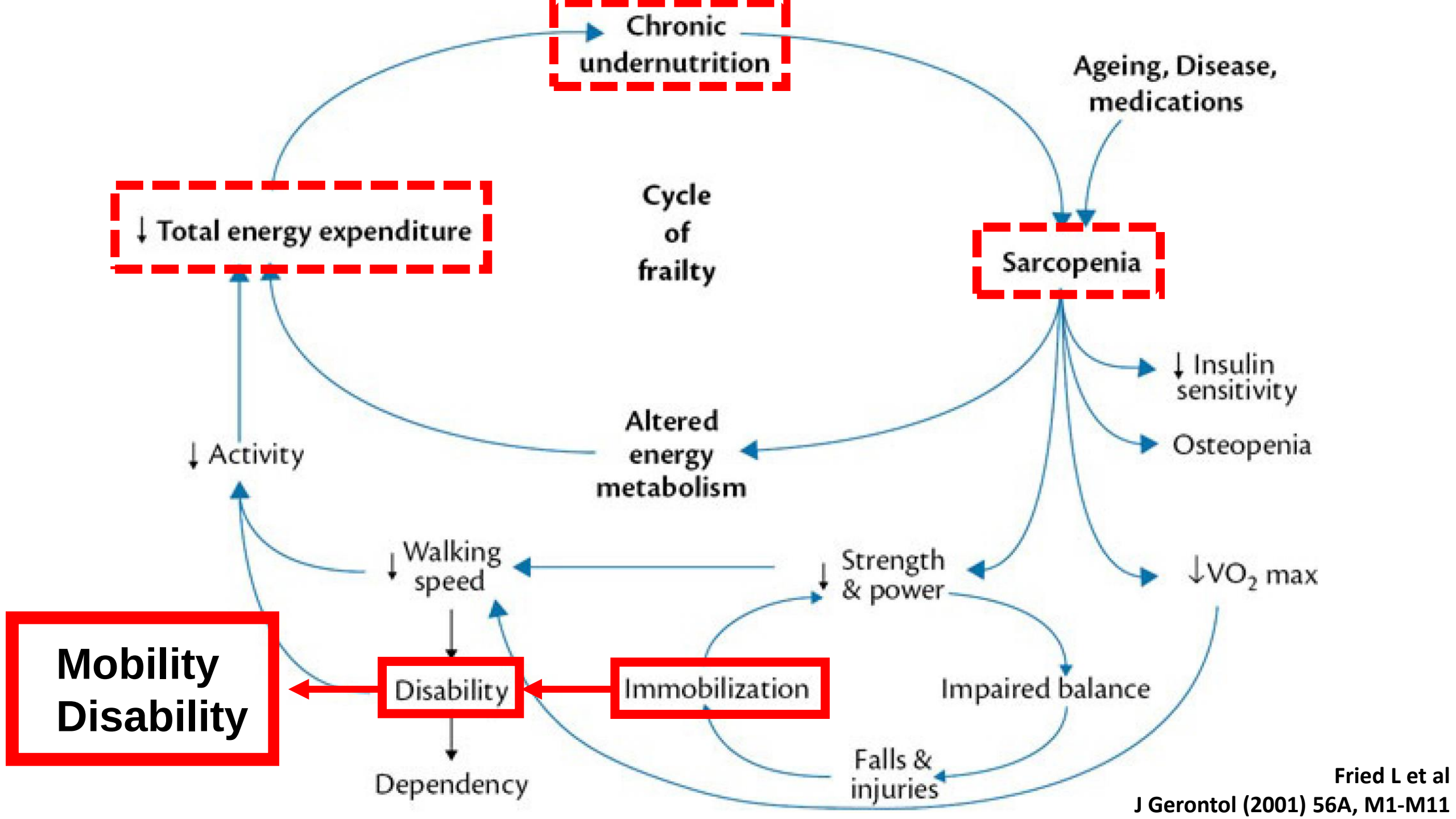
Gingrich et al. BMC Geriatrics (2019) 19:120

PREVALENCE AND OVERLAP OF COMORBIDITY, DISABILITY, AND FRAILTY AMONG COMMUNITY-DWELLING MEN AND WOMEN 65 YEARS AND OLDER PARTICIPATING IN THE CARDIOVASCULAR HEARTH STUDY



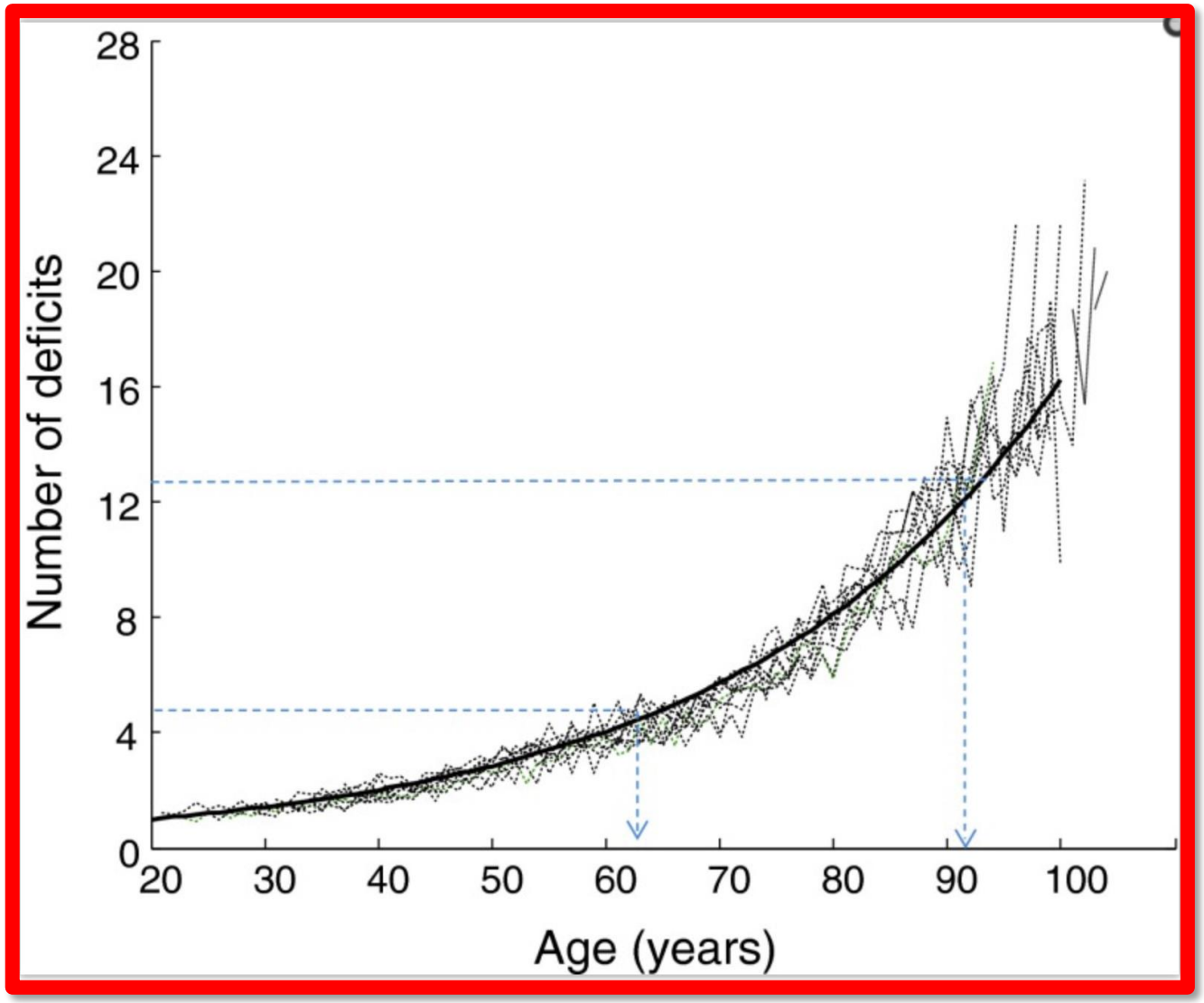
27,2%

Fried L et al
J Gerontol (2004) VOL. 59 N° 3, 253-265



Fried L et al
J Gerontol (2001) 56A, M1-M11

AGE TRAJECTORIES OF THE MEAN NUMBER OF DEFICITS



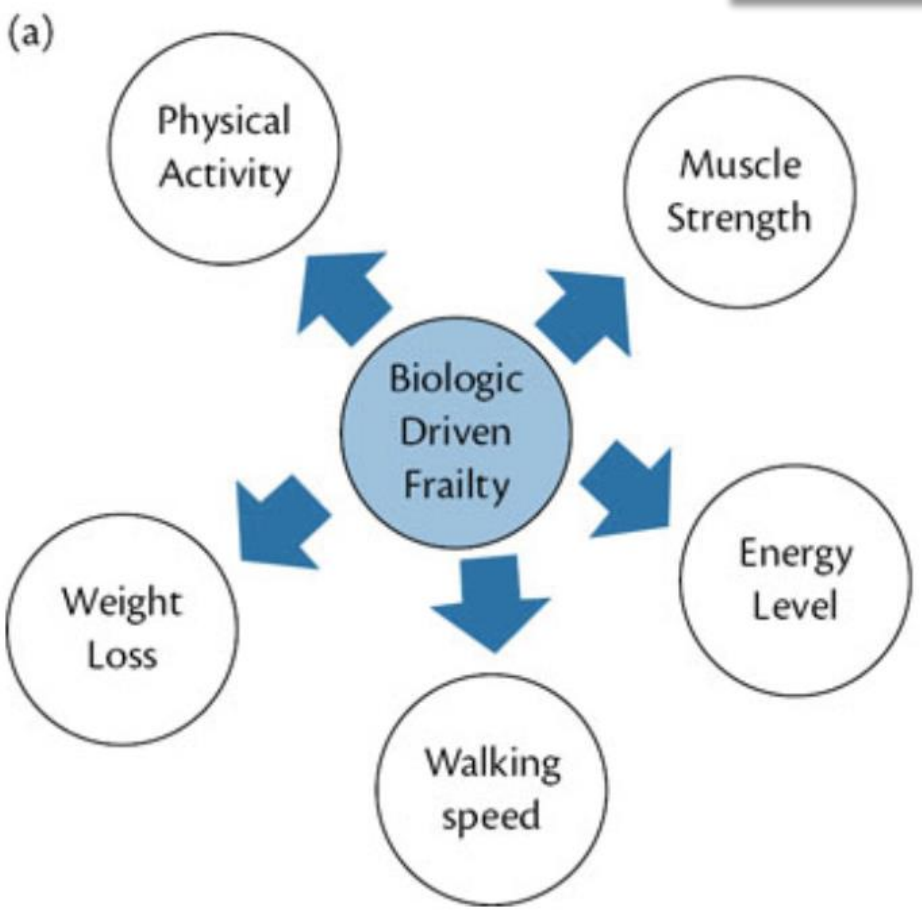
Mitnitski

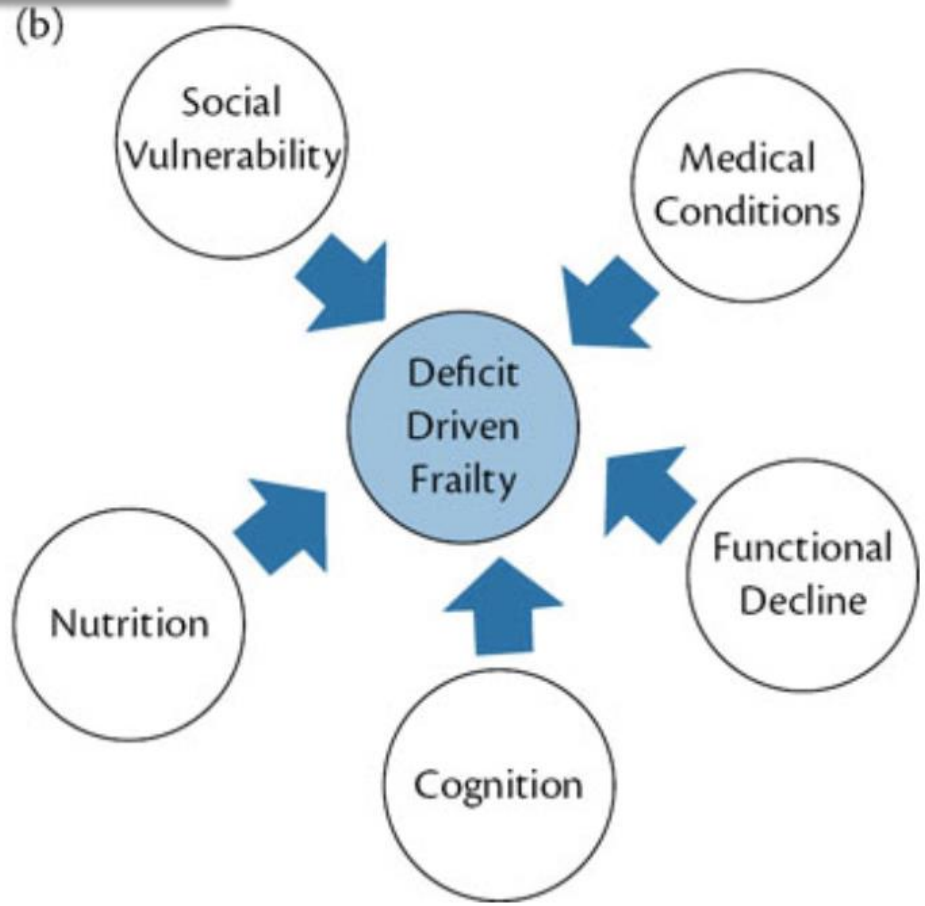
TWO MOST COMMON CONCEPTUALIZATIONS OF FRAILTY

Frailties

Cognitive-Psychological-Social Domains

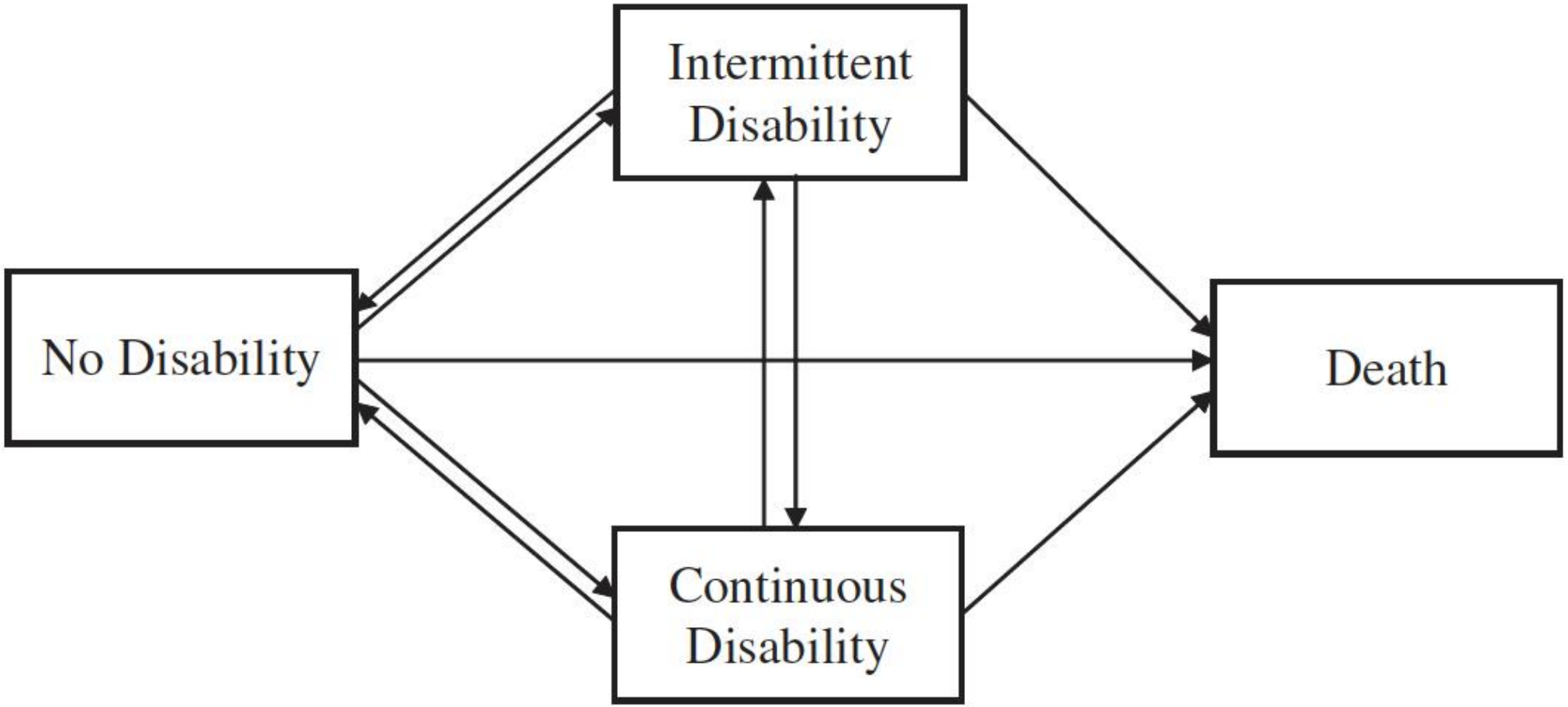
Oxford Textbook of Geriatric Medicine 3° EDITION - 2018





Fried L et al
J Gerontol (2001) 56A, M1-M11

Rockwood et al
The ScientificWorld (2001) 1, 326-336



Gill TM et al J Am Geriatr Soc 54:248–254, 2006

ELSEVIER

JAMDA

journal homepage: www.jamda.com

Special Article

Frailty Consensus: A Call to Action

1. A previous consensus conference on frailty agreed "on the usefulness of defining frailty in clinical settings"
2. Other areas in which they had more than 80% agreement included that frailty is a clinical syndrome:
   - Not disability
   - Increased vulnerability in which minimal stress can cause functional impairment
   - Might be reversible or attenuated by interventions
   - Mandatory for health workers to detect as soon as possible
   - Useful in primary and community care
3. However, the conference failed to recommend a clear course forward because of an inability to agree on a "single operational definition of frailty that can satisfy all experts." The heterogeneity of that consensus group may have contributed to the inability to come to a firm conclusion.

Morley JE et al JAMDA 14 (2013) 392e397

Phenotype of Frailty: Characterization in the Women's Health and Aging Studies

Background.

"Frailty" is an adverse, primarily gerontologic, health condition regarded as frequent with aging and having severe consequences. Although clinicians claim that the extremes of frailty can be easily recognized, a standardized definition of frailty has proved elusive until recently. This article evaluates the cross-validity, criterion validity, and internal validity in the Women's Health and Aging Studies (WHAS) of a discrete measure of frailty recently validated in the Cardiovascular Health Study (CHS).

Methods.

The frailty measure developed in CHS was delineated in the WHAS data sets. Using latent class analysis, we evaluated whether criteria composing the measure aggregate into a syndrome. We verified the criterion validity of the measure by testing whether participants defined as frail were more likely than others to develop adverse geriatric outcomes or to die.

Bandeen-Roche K et al Journal of Gerontology: MEDICAL SCIENCES 2006, Vol. 61A, No. 3, 262–26

Conditional Probabilities of Meeting Criteria Within Latent Frailty Classes: WHAS*

	2-Class Model		3-Class Model		
	Class 1	Class 2	Class 1	Class 2	Class 3
Criterion	Nonfrail	Frail	Robust	Intermediate	Frail
Weight loss	.073	.26	.072	.11	.54
Weakness	.088	.51	.029	.26	.77
Slowness	.15	.70	.004	.45	.85
Low physical activity	.078	.51	.000	.28	.70
Exhaustion	.061	.34	.027	.16	.56
Class prevalence (%)	73.3	26.7	39.2	53.6	7.2

Bandeen-Roche K et al Journal of Gerontology: MEDICAL SCIENCES 2006, Vol. 61A, No. 3, 262–26

Association of Baseline Frailty Status and Risk of Incident Adverse Events

Outcome	Adjusted HRs (95% CIs)†	
	Intermediate‡	Frail‡
Fall ($n = 560$)	0.92 (0.63, 1.34)	1.18 (0.63, 2.19)
Severe ADL disability ($n = 612$)	5.68 (2.41, 13.42)	15.79 (5.83, 42.78)
Severe IADL disability ($n = 698$)	3.53 (1.20, 10.35)	10.44 (3.51, 31.00)
Hospitalization ($n = 715$)	0.99 (0.67, 1.47)	0.67 (0.33, 1.35)
Permanent nursing home entry ($n = 750$)§	5.16 (0.81, 32.79)	23.98 (4.45, 129.2)
Death ($n = 766$)	3.50 (1.91, 6.39)	6.03 (3.00, 12.08)

Bandeen-Roche K et al Journal of Gerontology: MEDICAL SCIENCES 2006, Vol. 61A, No. 3, 262–26

the inherent characteristics of the frailty syndrome: a system-wide syndrome that demands a system-wide approach.

Effects of multi-domain interventions in (pre)frail elderly on frailty, functional, and cognitive status: a systematic review

Dedeyne L et al Clinical Interventions in Aging 2017:12 873–896

Background:
Treatment for frailty focuses on multi-domain interventions to target multiple affected functions in order to decrease the adverse outcomes of frailty. No systematic reviews on the effectiveness of multi-domain interventions exist in a well-defined frail population.

Objectives:
This systematic review aimed to determine the effect of multi-domain compared to mono-domain interventions on frailty status and score, cognition, muscle mass, strength and power, functional and social outcomes in (pre)frail elderly (>65 years).

Results:
Twelve studies were included,

Study	Country	Study participants	Duration of the intervention	Measurements						Study design	N	Frailty diagnostic tool
				Intervention period			Follow-up period					
				Pre	3 months before end of intervention	Post (0 months)	3–4 months	6 months	9 months			
Chan et al[32]	Taiwan	(Pre)frail, men and women, aged 71.4 (±3.7)	3 months	*		*	*		*	RCT	117	3–6 on The Chinese Canadian Study of Health and Aging Clinical Frailty Scale Telephone Version AND ≥1 of modified Fried frailty phenotype criteria[b]
Chin A Paw et al[33,34,39] and De Jong et al[35–38,40]	The Netherlands	Frail, men and women, aged 79[a]	17 weeks	*		*				RCT	112–161	Modified Chin A Paw frailty definition[c]
Hennessey et al[41]	United States	Moderately frail, men and women, aged 71.3 (±4.5)	6 months	*		*				RCT	31	Physical performance test (PPT): score (12–28)/36[d]
Ikeda et al[55]	Japan	(Pre)frail, men and women, aged 78.4±7.8 and 80.4±8.9	3 months	*		*				Cross-over	52	Fried frailty phenotype criteria[e]
Kenny et al[42]	United States	Frail, women, aged 76.6 (±6.0)	6 months	*		*				RCT	99	At least 1 of 5 Fried frailty criteria: population is at least prefrail[e]
Kim et al[43]	Japan	Frail, women, aged 75+	3 months	*		*	*			RCT	131	At least 3 of the modified Fried frailty phenotype criteria[f]
Kwon et al[44]	Japan	Prefrail, women, aged 76.8	3 months	*		*		*		RCT	89	Modified Fried frailty phenotype criteria[g]
Luger et al[53]	Austria	(Pre)frail, men and women, aged 82.8 (±8.0)	12 weeks	*		*				RCT	80	Prefrail or frail according to Frailty Instrument for Primary Care of the Survey of Health, Ageing, and Retirement in Europe (SHARE-FI)[h]
Ng et al[45]	Singapore	(Pre)frail, men and women, aged 70.0 (±4.7)	6 months	*	*	*		*		RCT	246	Fried frailty phenotype criteria[e]
Rydwik et al[46–48] Lammes et al[49]	Sweden	Frail, men and women, aged 83.3 (±4.0)	9 months	*		*		*		RCT	96	Modified Chin A Paw frailty definition[c]
Tarazona-Santabalbina et al[54]	Spain	Frail, men and women, aged 70+	24 weeks	*		*				RCT	100	Fried frailty phenotype criteria[e]
Tieland et al[50] and Van de Rest et al[51]	The Netherlands	(Pre)frail, men and women, aged 78 (±1.0)	24 weeks	*		*				RCT	62	1–2 (prefrail) or at least 3 (frail) of the Fried frailty phenotype criteria[e]

Inclusion and exclusion criteria

The inclusion criteria are as follows:

1) randomized controlled trials, quasi-experimental studies, or prospective or retrospective cohort studies with control groups;
2) testing of a multi-domain intervention to prevent or treat frailty in people aged >65 years;
3) classification in terms of (pre)frailty status according to an operationalized definition; and
4) primary outcomes including one or more of the following: frailty status or score, muscle mass, strength or power, physical functioning, and cognitive or social outcomes.

A multi-domain intervention was defined as an intervention that intervenes in at least two different domains, including exercise therapy (Ex), nutritional intervention (supplementation of proteins [NuP], supplementation of vitamins and minerals [NuVM], milk fat globule membrane [NuMF], or nutritional advice [NuAd]), hormone (Hor), cognitive (Cog) or psychosocial (PS) interventions.

Dedeyne L et al Clinical Interventions in Aging 2017:12

Conclusions

First, heterogeneous populations are considered as (pre)frail elderly as a broad spectrum of frailty screening tools is used in research and clinical practice.

Second, following questions arise: "What is the optimal moment to tackle frailty by an intervention (preventive or in early pre-frailty stage)?" and "How can participants be motivated to adhere to the intervention program (personal characteristics, program factors, environmental factors)?"

Dedeyne L et al Clinical Interventions in Aging 2017:12

What are the most effective interventions to improve physical performance in pre-frail and frail adults? A systematic review of randomised control trials

BACKGROUND:
With life expectancy continuing to rise in the United Kingdom there is an increasing public health focus on the maintenance of physical independence among all older adults. Identifying interventions that improve physical outcomes in pre-frail and frail older adults is imperative.

METHODS:
A systematic review of the literature 2000 to 2017 following PRISMA guidelines and registered with PROSPERO (no. CRD42016045325).

ENROLLED STUDIES
Ten RCT trials fulfilled selection criteria and quality appraisal.

Kidd et al. BMC Geriatrics (2019) 19:184

Author (Year)	Sample Size	Age Mean ± SD	Frailty criteria	Frailty status at baseline
[6]	53 (I) 49 (C)	84 84	Gait speed of less than 0.8 m/s PASE score of less than 64 for men and 52 for women.	Mixed (NF, PF, F).
[8]	120 (I) 121(C)	83.4 ± 5.81 83.2 ± 5.9	≥3 CHS criteria	Frail
[20]	120 (I) 121 (C)	83.4 ± 5.81 83.2 ± 5.9	≥3 CHS Criteria	Frail
[24]	22 (1) 19 (C)	84.1 ± 3.0 83.9 ± 2.8	≥10s to perform a rapid-gait test. Unable to stand up 5x from seated position). Self-reported exhaustion.	Frail
[35]	196 (I) 50 (C)	69.7 ± 4.23 70.15 ± .2.0	CHS frailty criteria	Mixed (pre-frail to frail)

Author (Year)	Sample Size	Age Mean ± SD	Frailty criteria	Frailty status at baseline
[48]	175 (I) 142 (C)	83.1 ± 5.8 83 ± 6.3	CGA	Mixed (NF, PF, F).
[49]	198 (I) 199 (C)	83.4 ± 5.4 83.2 ± 6.4	CGA	Mixed (NF, PF, F)

Author (Year)	Sample Size	Age Mean ± SD	Frailty criteria
[50]	31 (I) 34 (C)	78 ± 1 81 ± 1	> 1 CHS Frailty Criteria
[51]	76 (I) 76 (C)	79.1 ± 6.4 80.7 ± 6.0	BBS ≤49/56 ≤ 1 falls in past 6 months.
[52]	77 (WN) 70 (W) 75 (C)	76.3 ± 5.9 75.8 ± 5.2 75.7 ± 6.5	CHS Frailty Criteria

Kidd et al. BMC Geriatrics (2019) 19:184

Eligibility criteria

Articles were included that comprised of:

1. RCTs reporting one or more observable measure of physical performance related to frailty criteria (e.g. gait speed, grip strength, physical activity levels, mobility, balance, muscle mass, body mass index) as this study design generally supports greater validity and causal inference
2. Pre-frail or frail adult participants, aged > 65 years.
3. Peer reviewed publications, available in English.

Studies were excluded IF:

1. Physical performance was only measured using Activities in Daily Living (ADL) or Instrumental Activities of Daily Living (IADL) to ensure physical frailty, rather than disability was assessed.
2. Participants were also excluded if they had dementia, psychosis/personality disorders, or were institutionally confined

Several factors related to intervention success:

1. firstly, interventions targeted to improve physical condition, e.g. resistance training to build muscle mass and strength, and a clearly defined outcome (e.g. upper or lower body strength) reported significant improvements.

2. Secondly, interventions combining resistance and balance training were most successful in treating physical symptoms associated with frailty, reducing falls, and maintaining health benefits. Combining different types of physical exercise may therefore support maximum impact on all physical performance components associated with frailty i.e. mobility, balance, body mass, levels of activity

3. Thirdly, supervised interventions across primary and secondary care reported improved physical performance.

4. The additional effect of combining physical exercise with a nutritional intervention is frequently observed, however not consistently

Kidd et al. BMC Geriatrics (2019) 19:184

Conclusion

the results tentatively suggest that tailored, supervised, physical activity interventions are effective at improving physical performance components associated with frailty in both primary and secondary care settings. However, until there is an agreed definition for frailty and a core set of measures to assess this, any attempt to create an optimal validated intervention will be impeded. This absence may ultimately impact on the ability of older and frail adults to live well and for longer in the community.

Kidd et al. BMC Geriatrics (2019) 19:184

J Nutr Health Aging. 2019;23(9):771-787

PHYSICAL FRAILTY: ICFSR INTERNATIONAL CLINICAL PRACTICE GUIDELINES FOR IDENTIFICATION AND MANAGEMENT

E. DENT[1,2], J.E. MORLEY[3], A.J. CRUZ-JENTOFT[4], L. WOODHOUSE[5], L. RODRÍGUEZ-MAÑAS[6], L.P. FRIED[7], J. WOO[8], I. APRAHAMIAN[9], A. SANFORD[3], J. LUNDY[10], F. LANDI[11], J. BEILBY[1], F.C. MARTIN[12], J.M. BAUER[13], L. FERRUCCI[14], R.A. MERCHANT[15], B. DONG[16], H. ARAI[17], E.O. HOOGENDIJK[18], C.W. WON[19], A. ABBATECOLA[20], T. CEDERHOLM[21], T. STRANDBERG[22,23], L.M. GUTIÉRREZ ROBLEDO[24], L. FLICKER[25], S. BHASIN[26], M. AUBERTIN-LEHEUDRE[27], H.A. BISCHOFF-FERRARI[28], J.M. GURALNIK[29], J. MUSCEDERE[30], M. PAHOR[31], J. RUIZ[32], A.M. NEGM[33], J.Y. REGINSTER[34], D.L. WATERS[35], B. VELLAS[36]

innovative medicines initiative

Europe's partnership for health

..... the IMI-JU identified in the vagueness of existing frailty definitions the major obstacle for the development of novel therapeutic interventions tackling the age-related muscle decline, a major cause of disability in older persons and relevant burden for public health systems.

Letter to the editor https://doi.org/10.1016/j.ejim.2019.01.007
call by the Innovative
Medicines Initiative - Joint Undertaking (IMI-JU)
https://www.imi.europa.eu/

Frailty 1

Frailty: implications for clinical practice and public health

Emiel O Hoogendijk, Jonathan Afilalo, Kristine E Ensrud, Paul Kowal, Graziano Onder, Linda P Fried

Lancet 2019; 394: 1365–75

Frailty 2

Management of frailty: opportunities, challenges, and future directions

Elsa Dent, Finbarr C Martin, Howard Bergman, Jean Woo, Roman Romero-Ortuno, Jeremy D Walston

Lancet 2019; 394: 1376–86

Over the past two decades, strategies to manage frailty have progressed substantially. However, to progress from traditional, episodic-based care to more proactive, person-centred care, we need to do much more.

Lancet 2019; 394: 1365–75

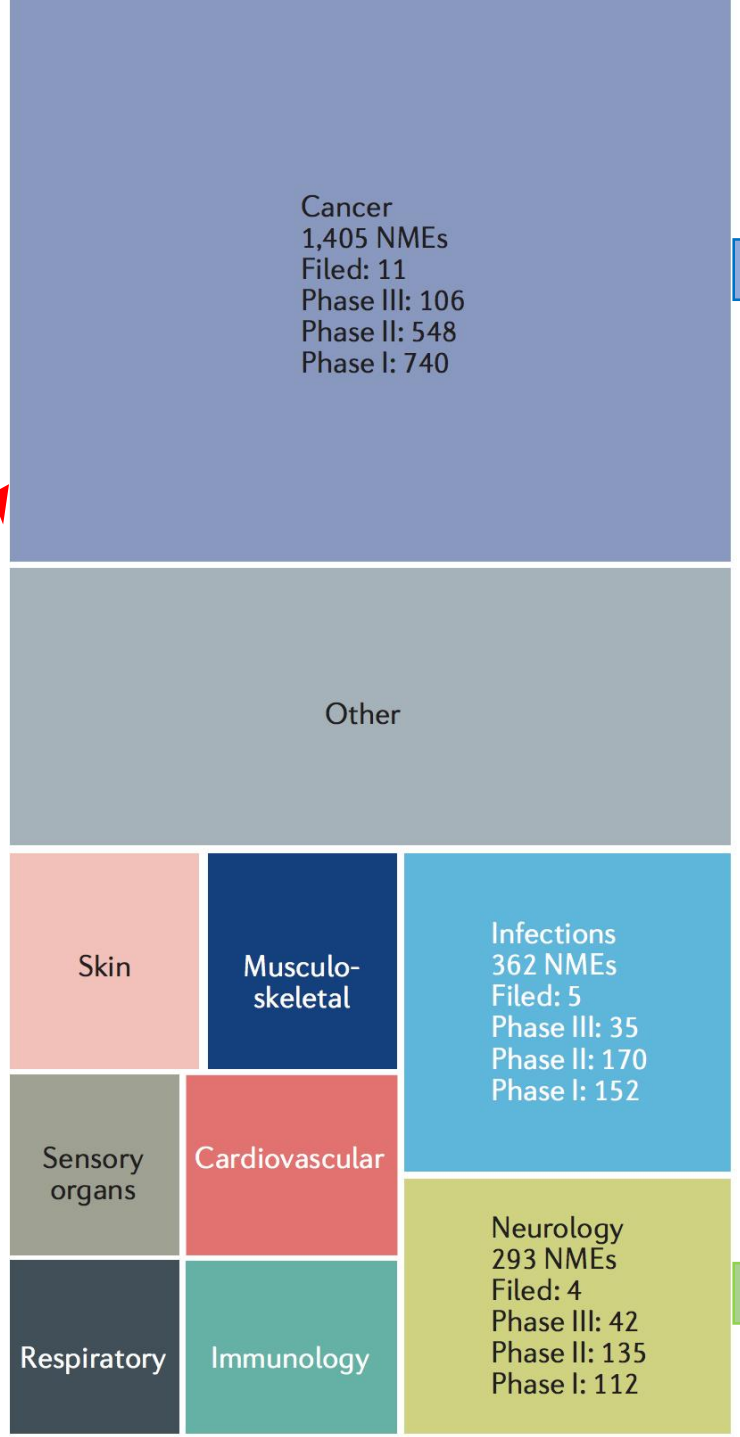
However, we recognise that a precision medicine approach in the context of frailty could be problematic, because multiple pathways across multiple physiological systems are involved.

Lancet 2019; 394: 1376–86

Therapeutic area focus of clinical-stage development programmes for new drugs

3,558
new molecular entities (NMEs)

40%



1405
NMEs

12
New approval
FDA 2018

112
NMEs for AD
Cummings 2018

0
New approval
FDA 2018

Moser J, Verdin P (2018)
Nature Reviews Drug Discovery, 17(10), 698–699

The “BIOmarkers associated with Sarcopenia and PHysical frailty in EldeRly pErsons” (BIOSPHERE) study: Rationale, design and methods

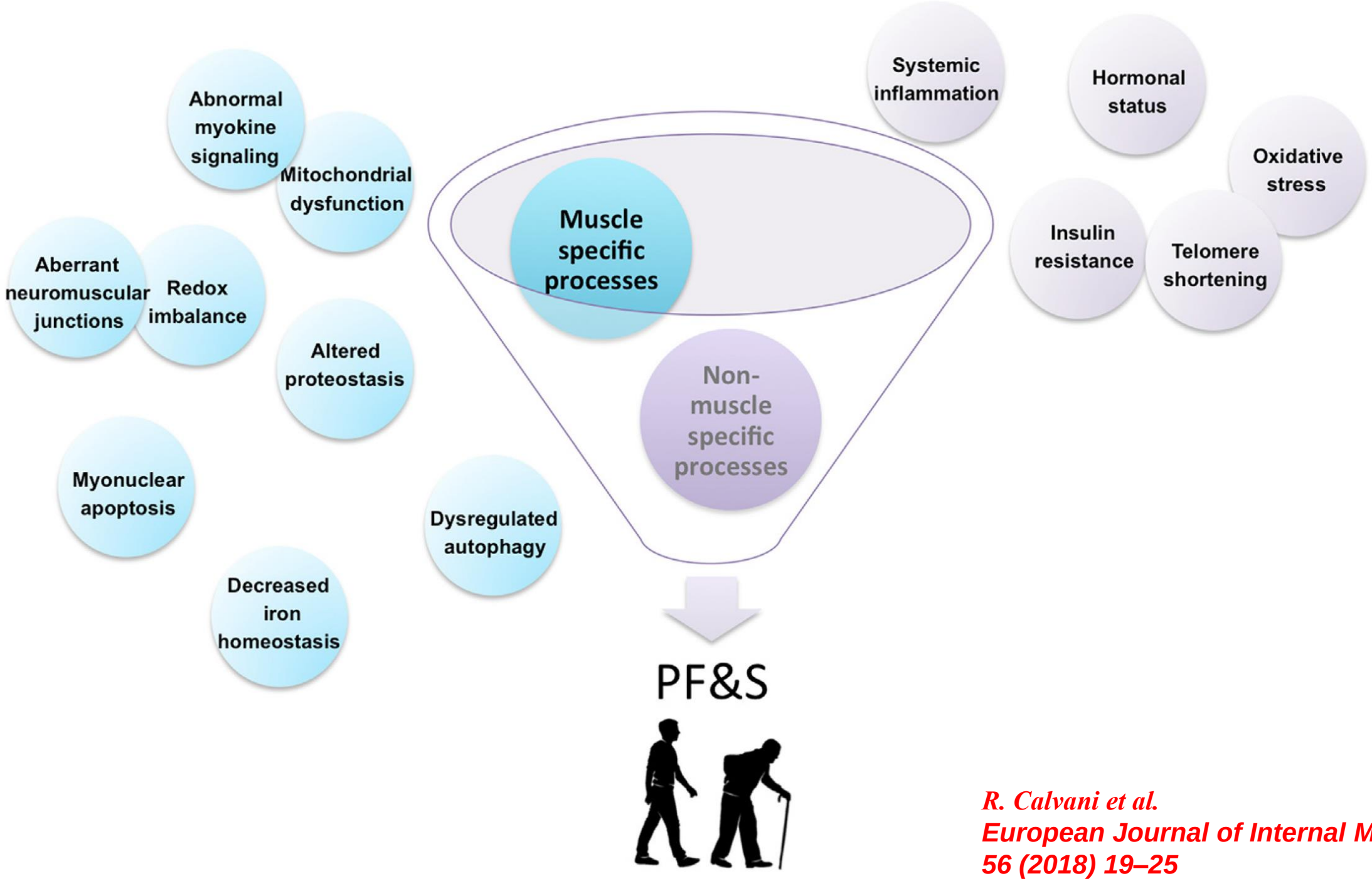
BACKGROUND

Sarcopenia, the progressive and generalised loss of muscle mass and strength/function, is a major health issue in older adults given its high prevalence and burdensome clinical implications. Over the years, this condition has been endorsed as a marker for discriminating biological from chronological age. However, the absence of a unified operational definition has hampered its full appreciation by healthcare providers, researchers and policymakers.

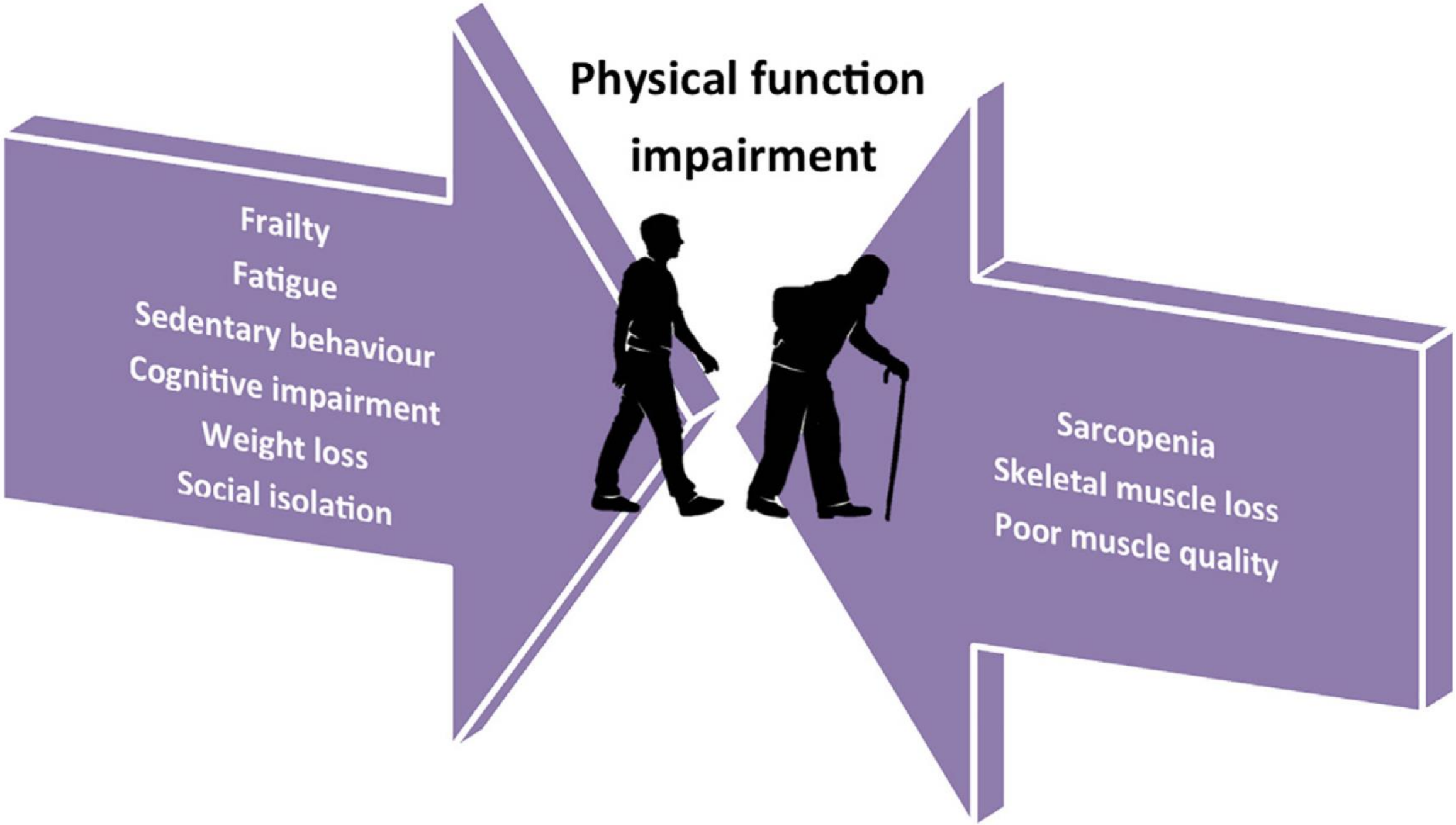
RATIONALE

The rationale, design and methods of the “BIOmarkers associated with Sarcopenia and PHysical frailty in EldeRly pErsons” (BIOSPHERE) study are described as an application of a multi-marker strategy for the development of biomarkers for the newly operationalised Physical Frailty & Sarcopenia condition.

R. Calvani et al. ***European Journal of Internal Medicine 56 (2018) 19–25***



R. Calvani et al.
European Journal of Internal Medicine 56 (2018) 19–25



R. Calvani et al. **European Journal of Internal Medicine 56 (2018) 19–25**

universal “one-size-fits-all”

vs

precision medicine approach
….patient centred