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# Frailty and Multimorbidity

RCCN Workshop: Inclusion of Older Adults in Clinical Research

February 24, 2021

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# Conflict of Interest Disclosure

I have no financial relationships with a commercial entity producing healthcare-related products and/or services consumed by or used on patients relevant to this presentation.

# Objectives

1. Describe varying definitions of multimorbidity and frailty
2. Review the relationship between multimorbidity and frailty and impact on outcomes
3. Discuss challenges and opportunities to the inclusion multimorbidity and frailty in clinical trials

# Definitions of Multimorbidity

## General

- “Total burden of biological dysfunction
- Sum of co-existing conditions
- Coexistence of two or more long term conditions
- Comorbidity indices such as Charlson, Elixhauser, Cumulative Illness Rating Scale, Charlson index, ACG System, Chronic Disease Score/RxRisk

## Implications

- *Many definitions of multimorbidity exist and most often a cut-off point of two or more is applied to a range of 4–147 different conditions.*
- *Diseases are included in all definitions of multimorbidity.*
- *Risk factors are often included in existing definitions, whereas symptoms and the severity of the conditions are less frequently included.*



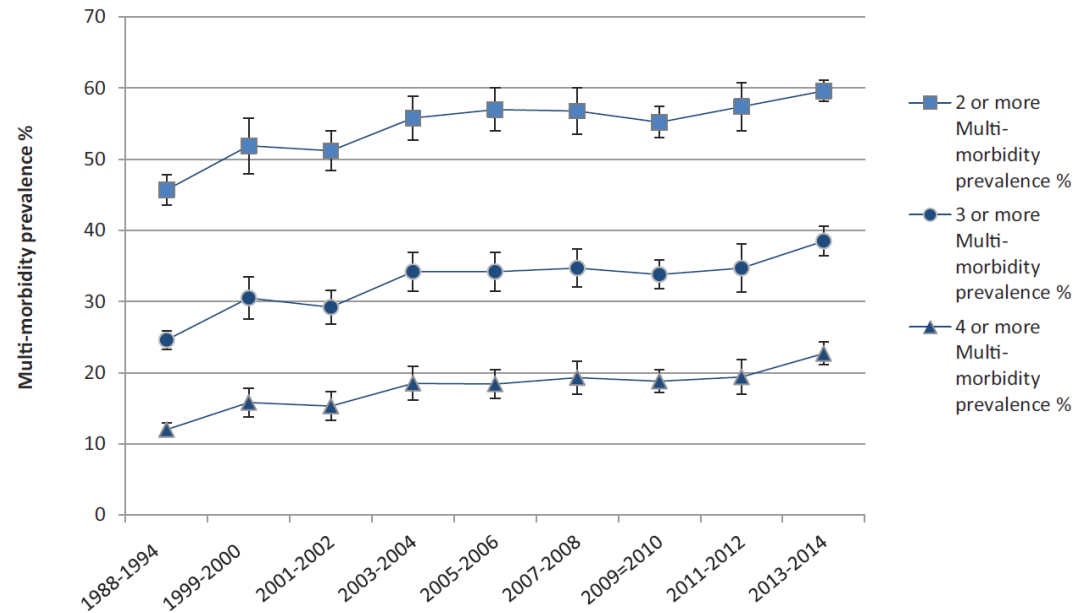
# The many faces of multimorbidity

- 80 YO with sarcoma, heart failure, kidney failure, severe pain, and existential crisis
- 70 YO who is bedbound with vascular dementia, renal insufficiency, lower extremity paraplegia s/p AAA repair with recurrent hospitalizations for anemia and... an exhausted caregiver
- 85 YO with DM2, CKD stage III/IV, h/o colon cancer, primary biliary cholangitis, osteoporosis with compression fractures, HTN, anxiety and dysthymia, GERD, obstructive sleep apnea, diminished hearing, asthma, and primary mild open angle glaucoma

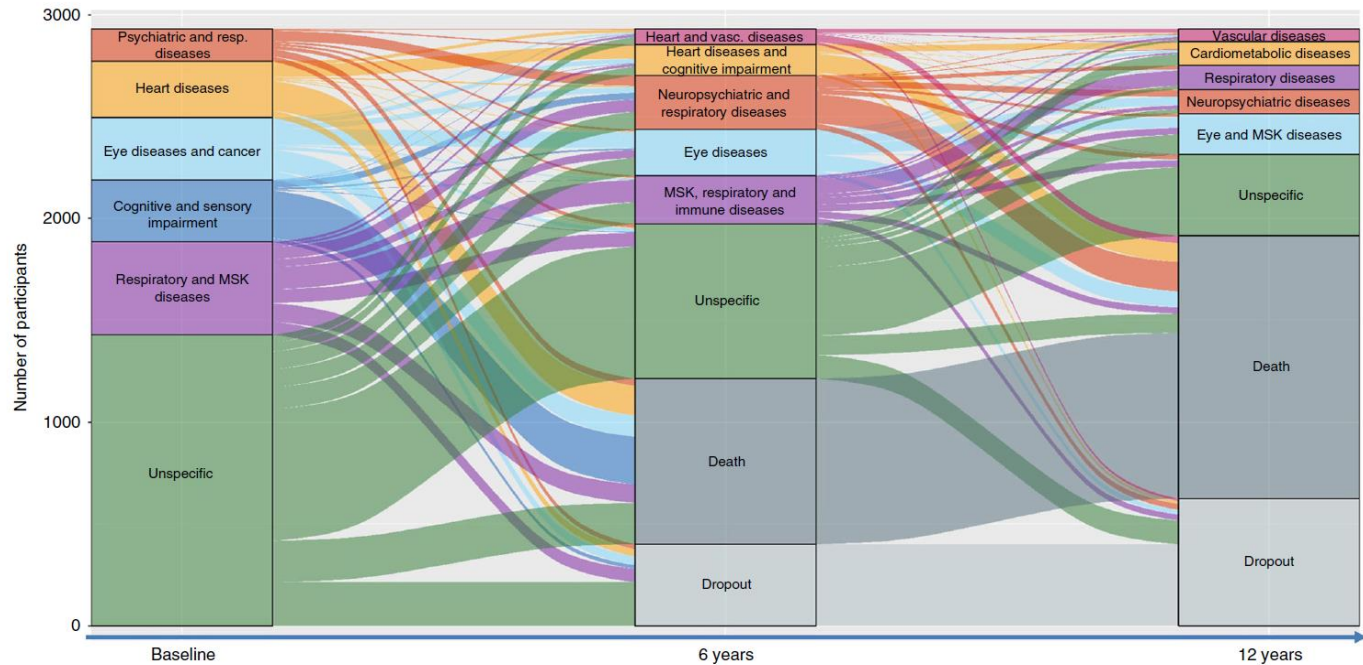
# Multimorbidity: Common and Growing

J Am Board Fam Med  
2018;31:503–513

Figure 1. Age-standardized trends in multi-morbidity prevalence for participants 20 years or older from NHANES 1988–2014 by number of comorbidities.



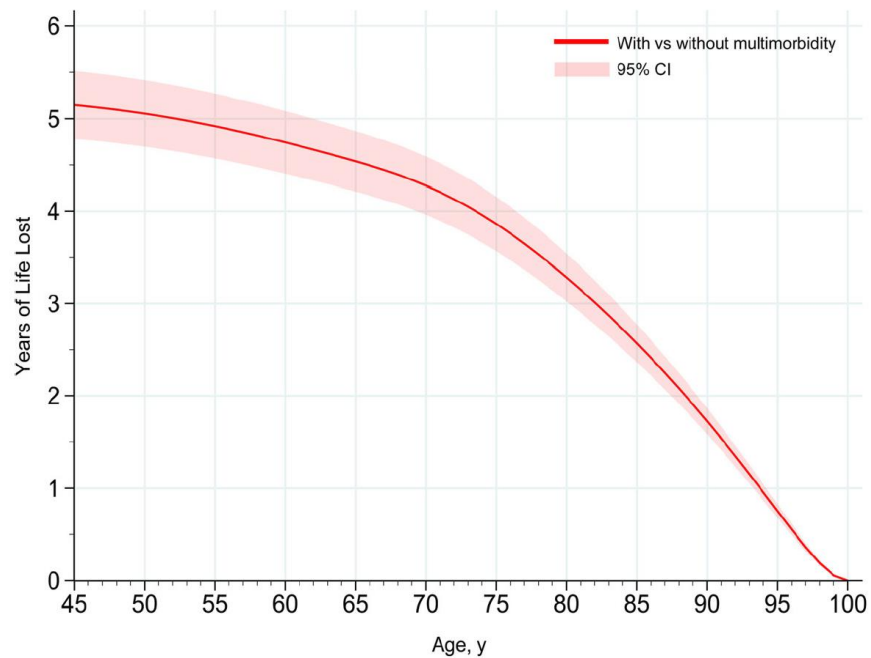
# Multimorbidity and Clinical Trajectories



Vetrano,  
et al. *Nat  
Commun*  
11, 3223  
(2020).

**Fig. 1 Evolution of multimorbidity clusters and clinical trajectories of older adults with multimorbidity over 12 years.** The height of the boxes and the thickness of the stripes are proportional to the amount of people belonging to the cluster and moving from the cluster, respectively. MSK musculoskeletal. To note, for this analysis participants were assigned to the cluster they were more likely to belong in order to investigate the most likely trajectories.

# Years of Life Lost due to Multimorbidity



CI=confidence interval; y=years.

Chudasama et al. *BMC Med* 17, 108 (2019).

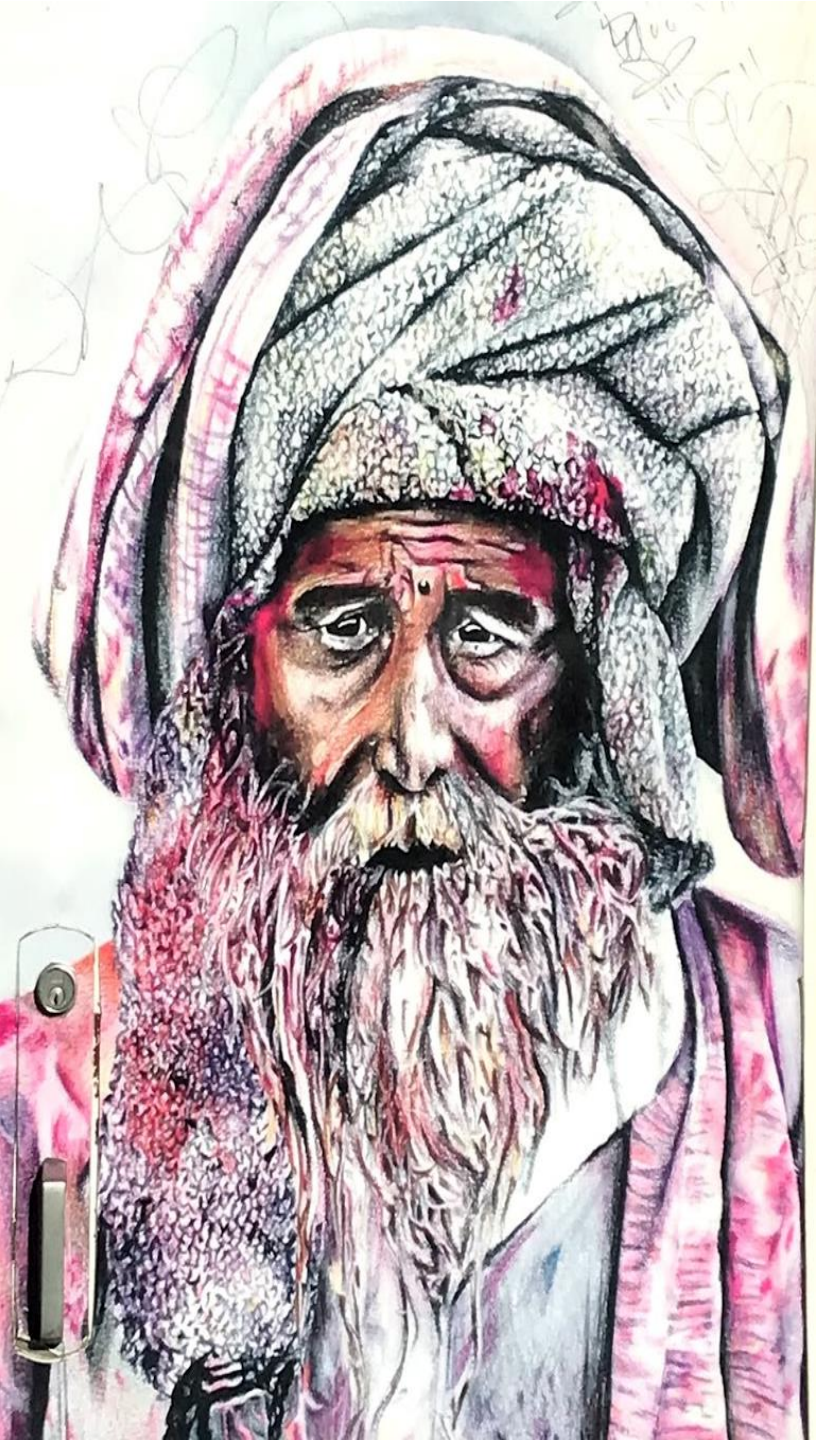
# Definitions of Frailty

## General

- “An aging-related syndrome of physiological decline, characterized by marked vulnerability to adverse health outcomes
- Five domains of nutritional status, energy, physical activity, mobility, and strength (Fried)
- Accumulation of deficits (Rockwood)
- Predisability (disability excluded)

## Implications

- *Little consensus on framework (38%) and even less on biomarkers (16%)*
- *Substantial discordance in classification between conceptual frameworks in the more intermediate levels of frailty*
- *? Differentiation between disability, comorbidity, and frailty*
- *Definitions require varying levels of participation and equipment*



# The many faces of frailty

86 YO with hypertension, degenerative joint disease, severe kyphosis of the thoracic spine, s/p right hip hemiarthroplasty, multiple falls, difficulty in rising unassisted from a seated position

78 YO with insulin requiring DM, hyperlipidemia, hypertension, cataracts. chronic pain due to severe bilateral knee osteoarthritis, and fatigue

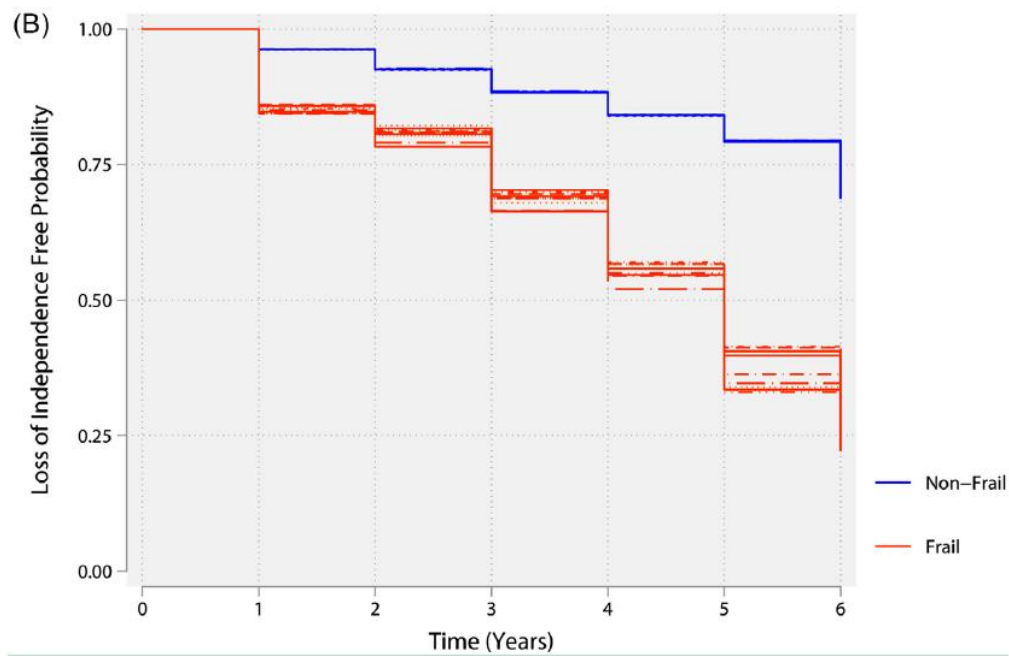
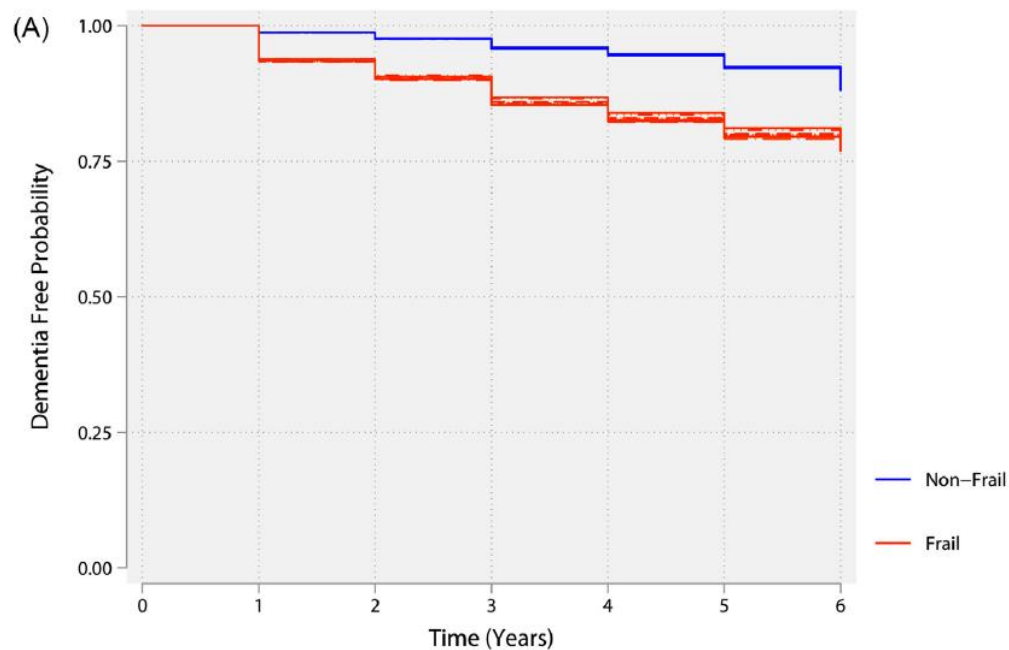
93 YO with early Alzheimer's disease who lives alone and appears unsteady on her feet

# Implications of Frailty

Frailty predicts

- loss of independence,
- activities of daily living disability and instrumental activities of daily living disability,
- mobility disability

Damluji et al. AJM 2020



# The Intersection of Frailty and Multimorbidity (MM)

- Multimorbidity correlates with frailty and vice versa.
- Frailty part of common distal pathway of multimorbidity
- Frailty has greater prognostic implications than MM
- Impact of an intervention is likely greater for frailty than MM

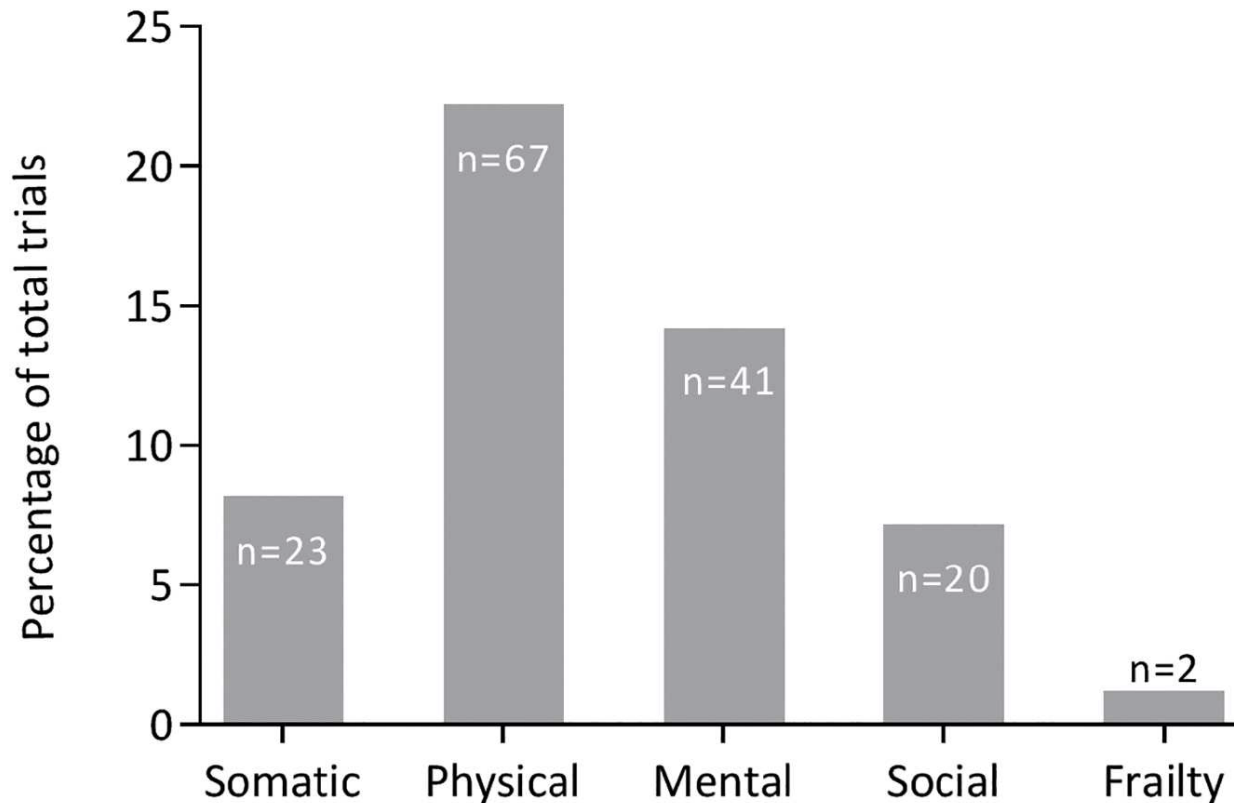
# Clinical Trials differentially Exclude Multimorbidity

- Review of all RCTs from Jan-March in 4 separate years in the 5 highest IF journals
- Multimorbidity was excluded in
  - 63% of the 284 RCTs identified
  - 90% of the 200 RCTs that mentioned coexisting diseases
  - 94% of the 190 RCTs that considered multimorbidity as part of the selection process.

# Clinical Trials Differentially Exclude Frailty

- Study of phase III or IV RCTs published in 2007
  - Exclusion criteria that may disproportionately affect those with frailty
    - Physical disability or functional limitations (18%)
    - Decreased life expectancy (22%)
    - Inability to give informed consent (11%)
    - Age-related cognitive impairment (5.5%)

# RCT's in Older Adults in 2012

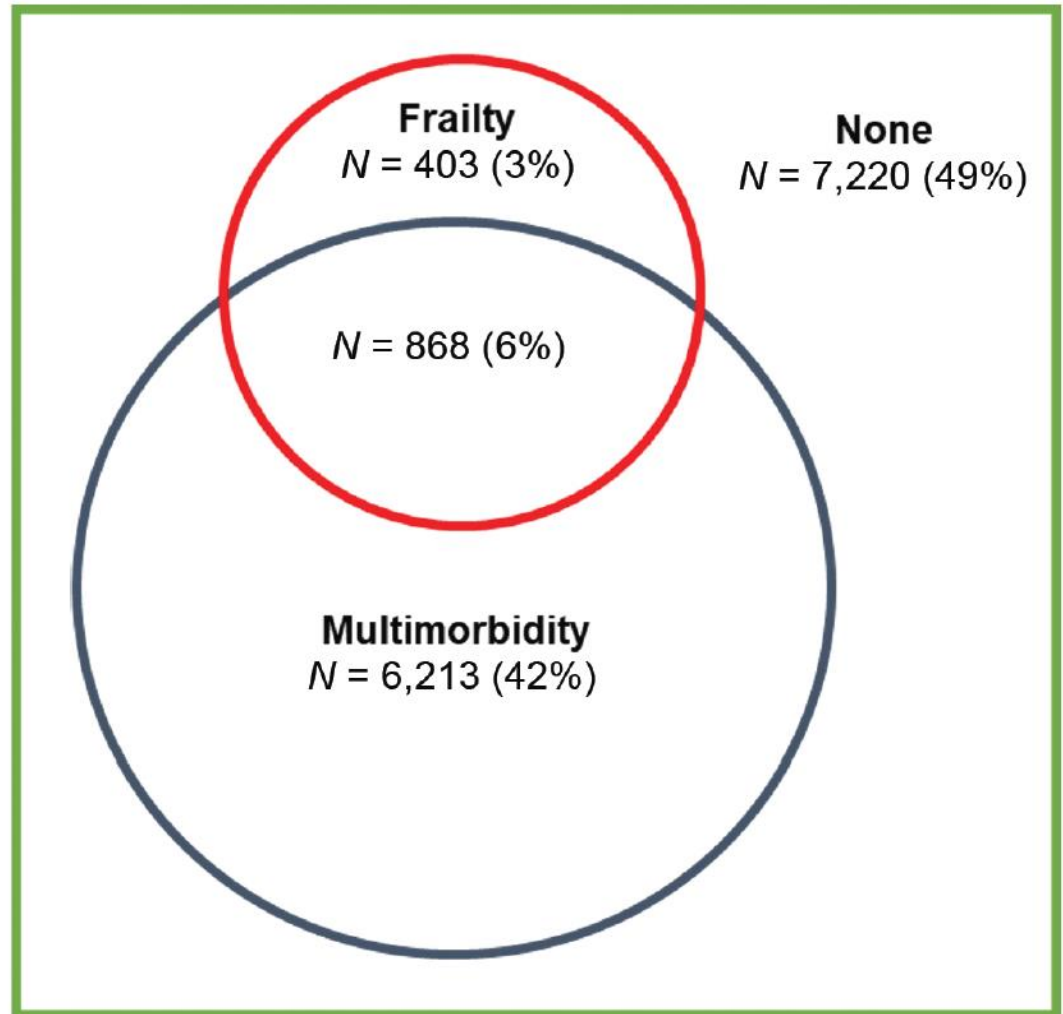


**Fig 3. Proportion of RCT's in older patients that report on different geriatric assessments\*.** Showing the distribution of different geriatric measurements and expressed as percentage of the total trials (n = 300).

\*Some articles reporting more than one domain: 14 articles reporting two geriatric domains, eight articles reporting three geriatric domains and only one article reports four geriatric domains.

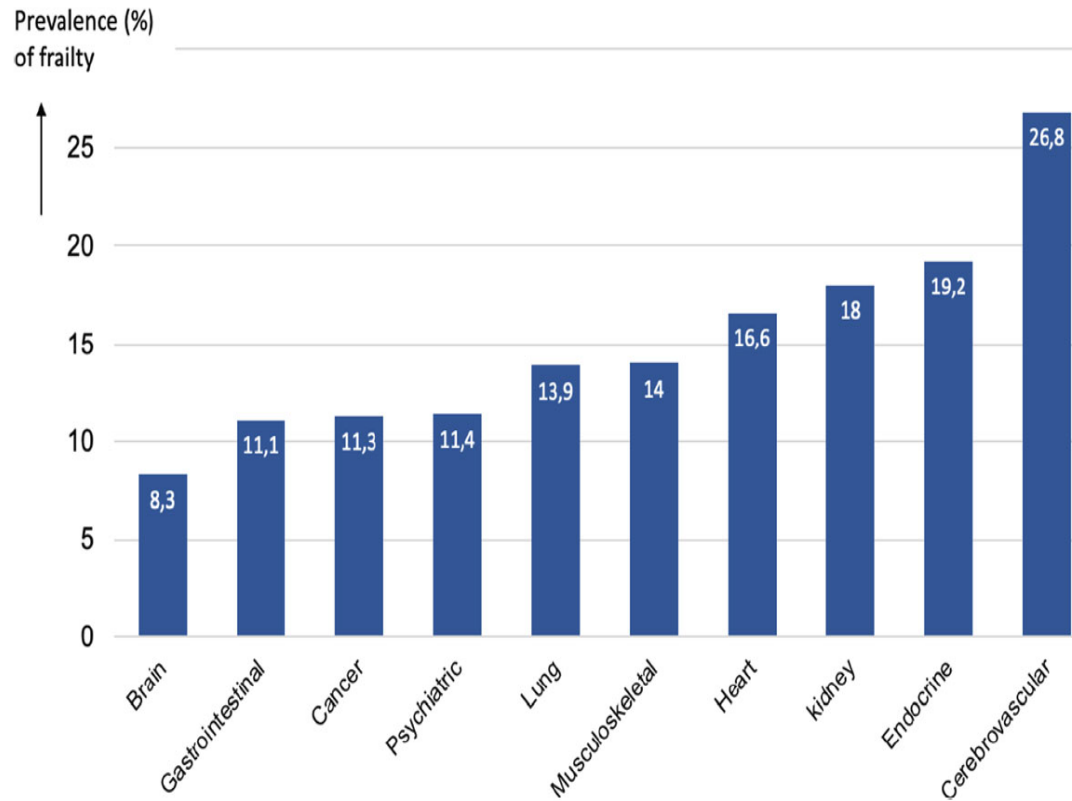
<https://doi.org/10.1371/journal.pone.0174053.g003>

# Frailty and Multimorbidity



Vetrano et al. J Gerontol A Biol Sci Med Sci.  
2019 Apr 23;74(5):659-666.

# Frailty and Multimorbidity Clusters



**Fig. 1** Prevalence of frailty (baseline FI-64  $\geq$  0.25) for each chronic disease cluster

# Multimorbidity, Frailty and 10-Yr Mortality

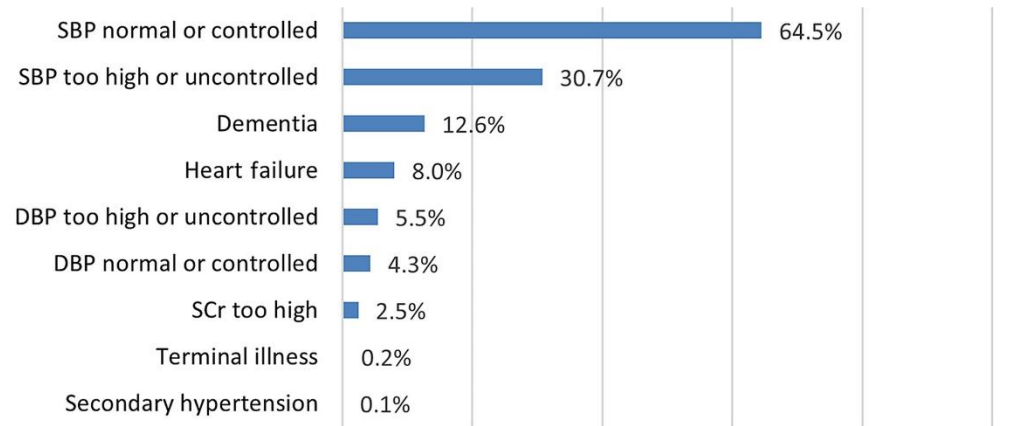
	Cox-regression analyses, model 1*			Cox-regression analyses, model 2**		
	HR	[95% CI]	<i>p</i>	HR	[95% CI]	<i>p</i>
<b>Combined model frailty with multimorbidity:</b>						
• Frailty index *100	1.05	[1.05–1.06]	< .001	1.05	[1.04–1.06]	< .001
• Multimorbidity	0.99	[0.95–1.03]	.568	1.00	[0.95–1.05]	.876
<b>Combined model frailty with all disease clusters:</b>						
• Frailty (yes/no)	2.01	[1.76–2.29]	< .001	1.84	[1.56–2.17]	< .001
• Psychiatric disorders	1.08	[0.96–1.21]	.209	0.99	[0.87–1.13]	.897
• Musculoskeletal diseases	0.84	[0.75–0.93]	.001	0.88	[0.78–0.99]	.033
• Brain diseases	0.92	[0.81–1.04]	.198	0.94	[0.82–1.07]	.358
• Lung disease	1.13	[0.99–1.28]	.069	1.09	[0.94–1.26]	.267
• Heart disease	1.08	[0.97–1.21]	.162	1.04	[0.91–1.19]	.549
• Endocrine disease	1.04	[0.91–1.20]	.554	0.99	[0.84–1.18]	.993
• Gastrointestinal diseases	1.10	[0.85–1.41]	.481	1.13	[0.86–1.48]	.375
• Cancer	1.84	[1.64–2.06]	< .001	2.16	[1.89–2.47]	< .001
• Cerebrovascular disease	1.34	[1.07–1.66]	.009	1.25	[0.94–1.66]	.124
• Kidney disease	1.59	[1.10–2.32]	.015	1.79	[1.21–2.65]	.003

\*Model 1 is adjusted for age, gender, and level of education

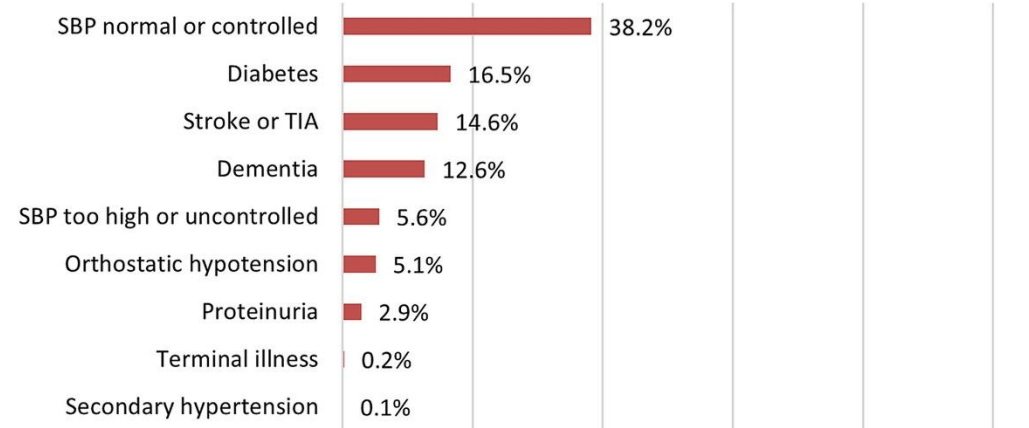
\*\*Model 2 is additionally adjusted for lifestyle characteristics (partner status, smoking, alcohol use, BMI)

# Generalizability of Blood Pressure Lowering Trials to Older Patients: Cross-Sectional Analysis

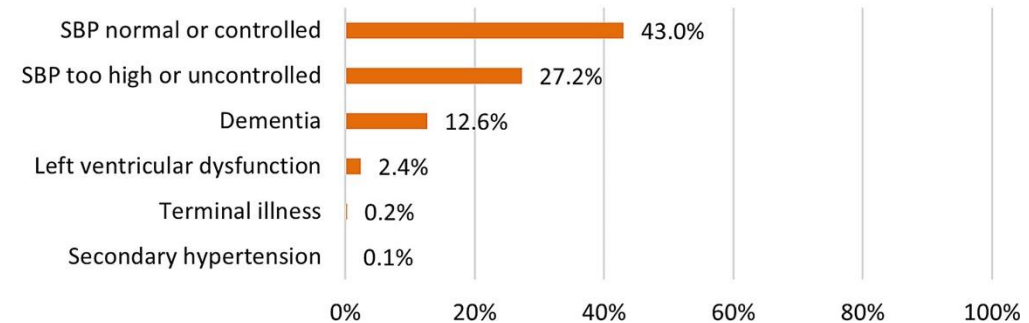
HYVET



SPRINT



OPTIMISE



# Challenges of Inclusion of Persons with Multimorbidity and/or Frailty

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- Prognostic uncertainty
- Drug-drug and drug-disease interactions
- Higher rates of mortality (reduction in outcomes ascertainment)



# Opportunities of Increased Inclusion of Persons with Multimorbidity and/or Frailty

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- Generalizability
- Reduction in subjective therapeutic nihilism
- Improved (shared) decision making
- Targeted prevention/treatments to improve outcomes
- Attention to nonmortality outcomes



# Take Home Messages



- Multimorbidity and frailty are both under-described in clinical trials
- Lack of standardized definitions impede comparisons and generalizability
- Routine standardized measures of frailty and MM in clinical trials will enhance decision making and reduce subjectivity in clinical care

Questions?

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