The webinar, "**The Global Importance of Frailty and Pre-Frailty in Middle-Aged Adults: A PURE Study,**" will begin shortly.

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CLSA Webinar Series

The Global Importance of Frailty and Pre-Frailty in Middle-Aged Adults: A PURE Study

Dr. Darryl Leong, McMaster University

12 to 1 PM ET | September 12, 2018

We traditionally consider the pathway from health to death to be mediated by the occurrence of disease. This research seeks to expand on this model by examining the role of frailty in promoting disease and death. This webinar will present preliminary results from an analysis of the Prospective Urban Rural Epidemiology (PURE) study, a prospective cohort study of over 130,000 middle-aged adults from 24 high-, middle-, and low-income countries from around the world.

This unique study will be one of the largest to investigate the role of frailty in disease and death in middle age. The on-going research will seek to prospectively identify important determinants and mechanisms of incident frailty. Our eventual goal is to develop strategies to prevent or reverse frailty.

The Global Importance of Frailty and Pre-Frailty in Middle-Aged Adults: A PURE Study

Darryl Leong

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The Population Health Research Institute

McMaster University and Hamilton Health Sciences

What is frailty?

- Aging-associated vulnerability to poor health outcomes when challenged by physiologic stressors

Xue, *Clin Geriatr Med* 2011; 27: 1

How can we measure frailty?

- >25 different scoring systems

How can we measure frailty?

Cumulative deficits

- Record presence/absence of >20 symptoms, physical signs, diseases, lab abnormalities
- The proportion of deficits exhibited = frailty index
  - <0.1 = non-frail
  - 0.1-0.21 = pre-frail
  - >0.21 = frail

Phenotype

- Low muscle strength
- Low physical activity
- Slow gait
- Unintentional weight loss
- Subjective exhaustion

- ≥3 = frail
- 1-2 = pre-frail

Biritwum *et al. Maturitas* 2016; 91: 8
Fried *et al. J Gerontol A Biol Sci Med Sci*. 2001; 56: M146

Cumulative Deficit Index – What Constitutes A Deficit?

Properties of "Deficits"

- Increase with age but do not saturate too early
- Associated with health
- Involve a range of bodily systems
- Deficits can be weighted, but most are binary

Searle *et al. BMC Geriatrics* 2008; 8: 24

Cumulative Deficit Index

Appropriate for Cumulative Deficit Index

- ≥30-40 deficits are desirable

E.g.

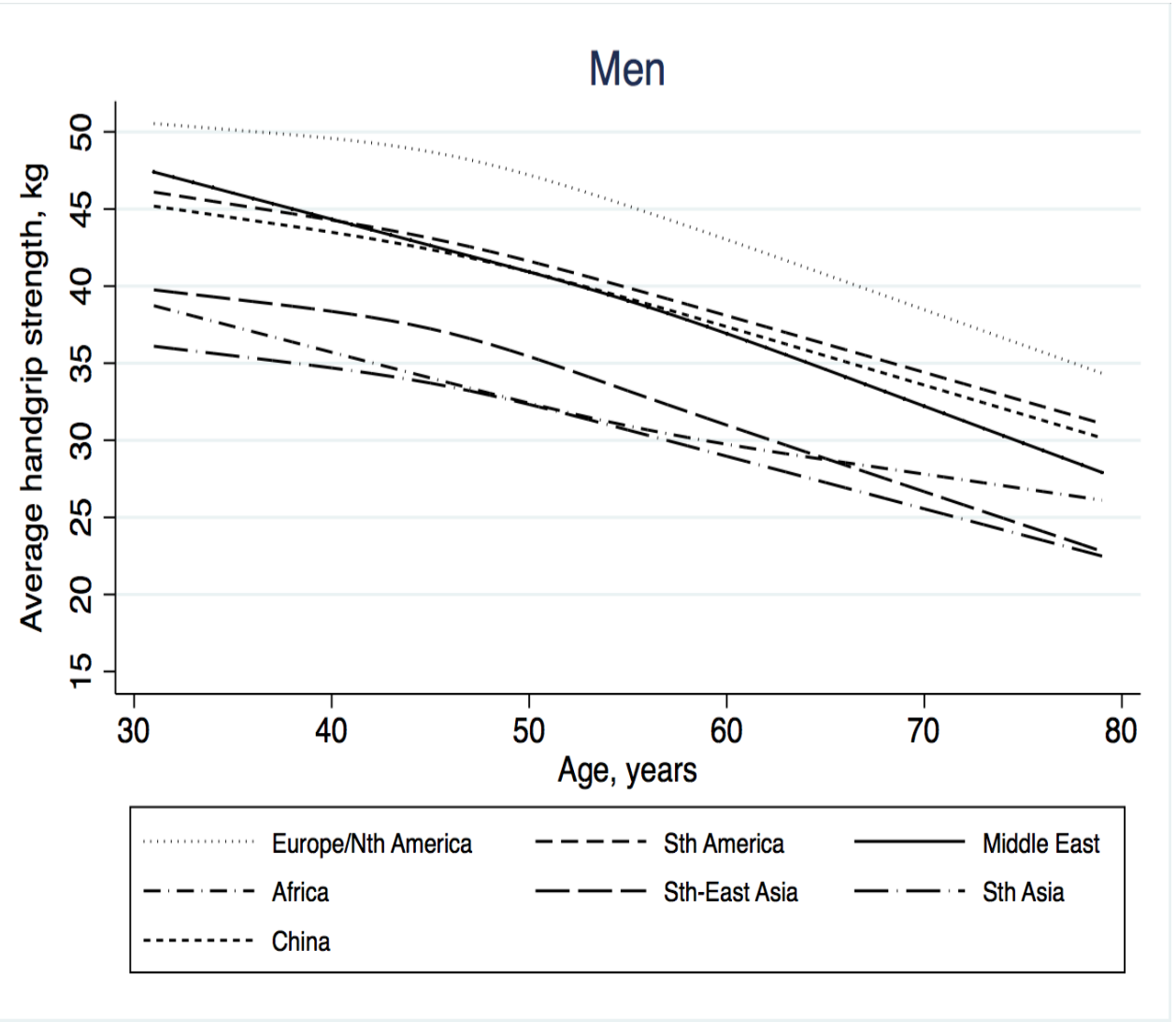
- Past history of cancer
- Feel depressed
- Need help dressing
- Grip strength

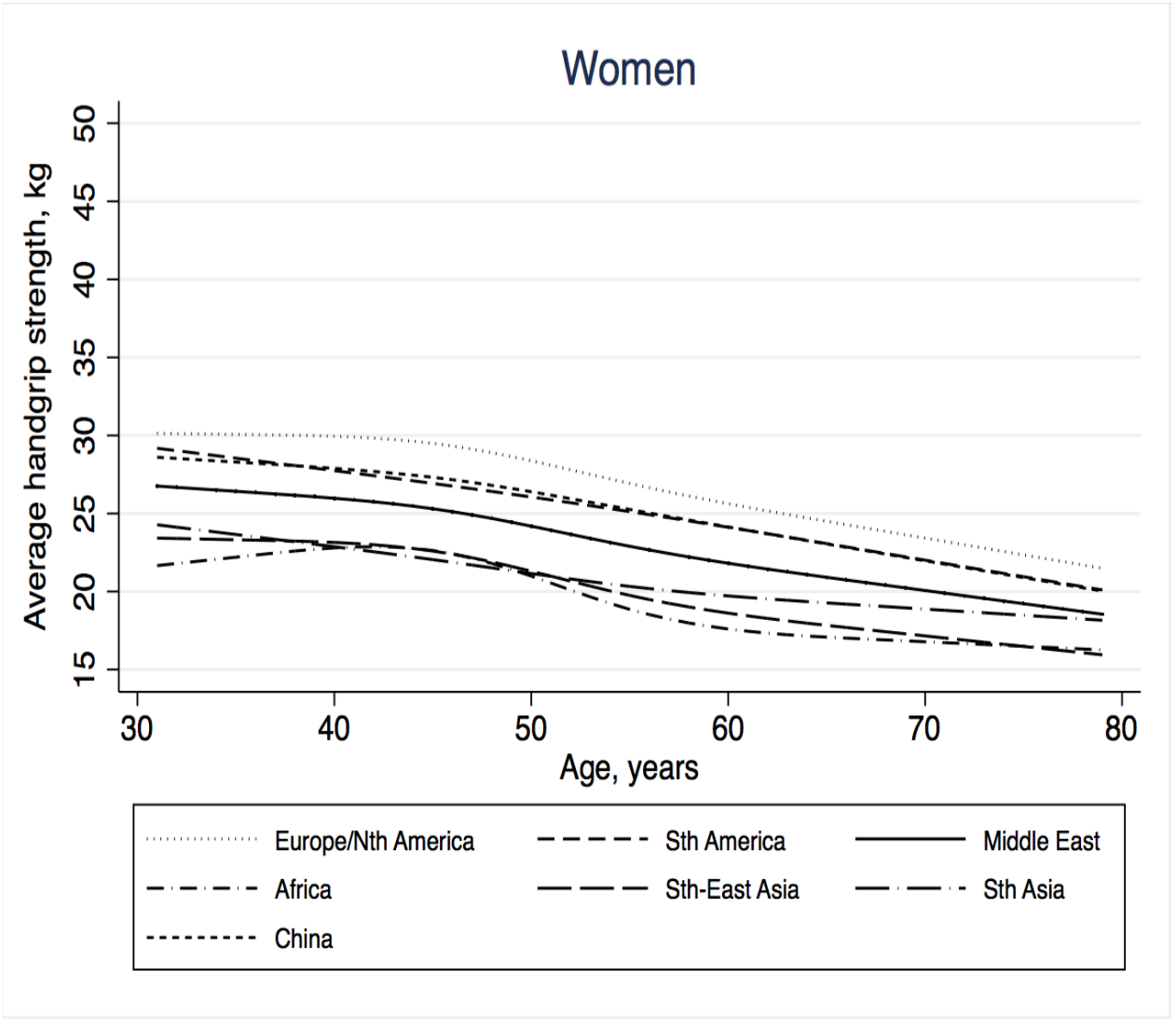
Not appropriate for Cumulative Deficit Index

- Needing spectacles
- Grey hair

Searle *et al. BMC Geriatrics* 2008; 8: 24

Frailty phenotype – low muscle strength





Leong *et al. J Cachexia Sarcopenia Muscle* 2016; 7: 535

Frailty phenotype – Physical activity

	High-income countries	Upper middle-income countries	Lower middle-income countries	Low-income countries
n	13,546	34,625	53,841	28,831
METxmin per week	3227 (1485-6426)	2436 (750-5979)	2340 (960-5177)	2520 (721-6442)

P-value for heterogeneity <0.0001
Lear *et al. Lancet* 2017; 390: 2643

How common is frailty?

- It depends
  - How it is measured
  - What population

Estimates of Frailty Prevalence

Study	Frailty Index	Domains Evaluated	Population	Frailty Prevalence
Rockwood	Older Americans Resources and Services Activities of Daily Living Scale	Activities of daily living; continence; cognitive function	Canadians aged ≥65 years N=9008	On scale 0-3 0 = 67% 1 = 12% 2 = 16% 3 = 5%
Woods	Fried phenotype	Muscle strength, gait speed, weight loss, exhaustion, physical activity	Women aged 60-79 years from US	28% pre-frail 16% frail
Cawthon	Cardiovascular Health Study	Shrinking, activity, weakness, slowness, low energy	Men aged ≥65 years from US	40% pre-frail 4% frail

Rockwood *et al. Lancet* 1999; 353: 205
Woods *et al. J Am Geriatr Soc*. 2005; 53: 1321
Cawthon *et al. J Am Geriatr Soc*. 2007; 55: 1216

Is frailty important?

Study	Frailty Index	Frailty Predictive Value for Death
Rockwood	Older Americans Resources and Services Activities of Daily Living Scale	On scale 0-3 0: RR = 1 1: RR = 1.2 (1.0-1.4) 2: RR = 2.0 (1.8-2.2) 3: RR = 3.1 (2.7-3.6)
Woods	Fried phenotype	Frail vs. non-frail: HR 1.71 (1.48-1.97)
Cawthon	Cardiovascular Health Study	Frail vs. non-frail: HR 2.05 (1.55-2.72)

Rockwood *et al. Lancet* 1999; 353: 205
Woods *et al. J Am Geriatr Soc*. 2005; 53: 1321
Cawthon *et al. J Am Geriatr Soc*. 2007; 55: 1216

What are the major knowledge gaps when it comes to frailty?

- Do different populations globally have different rates of frailty?
- Does frailty begin prior to ”older” age?
- *How* does frailty lead to premature death?
  - Does frailty lead to disease?
  - Does frailty lead to death independently of disease?

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Frailty in Middle-Income Countries – A Systematic Review

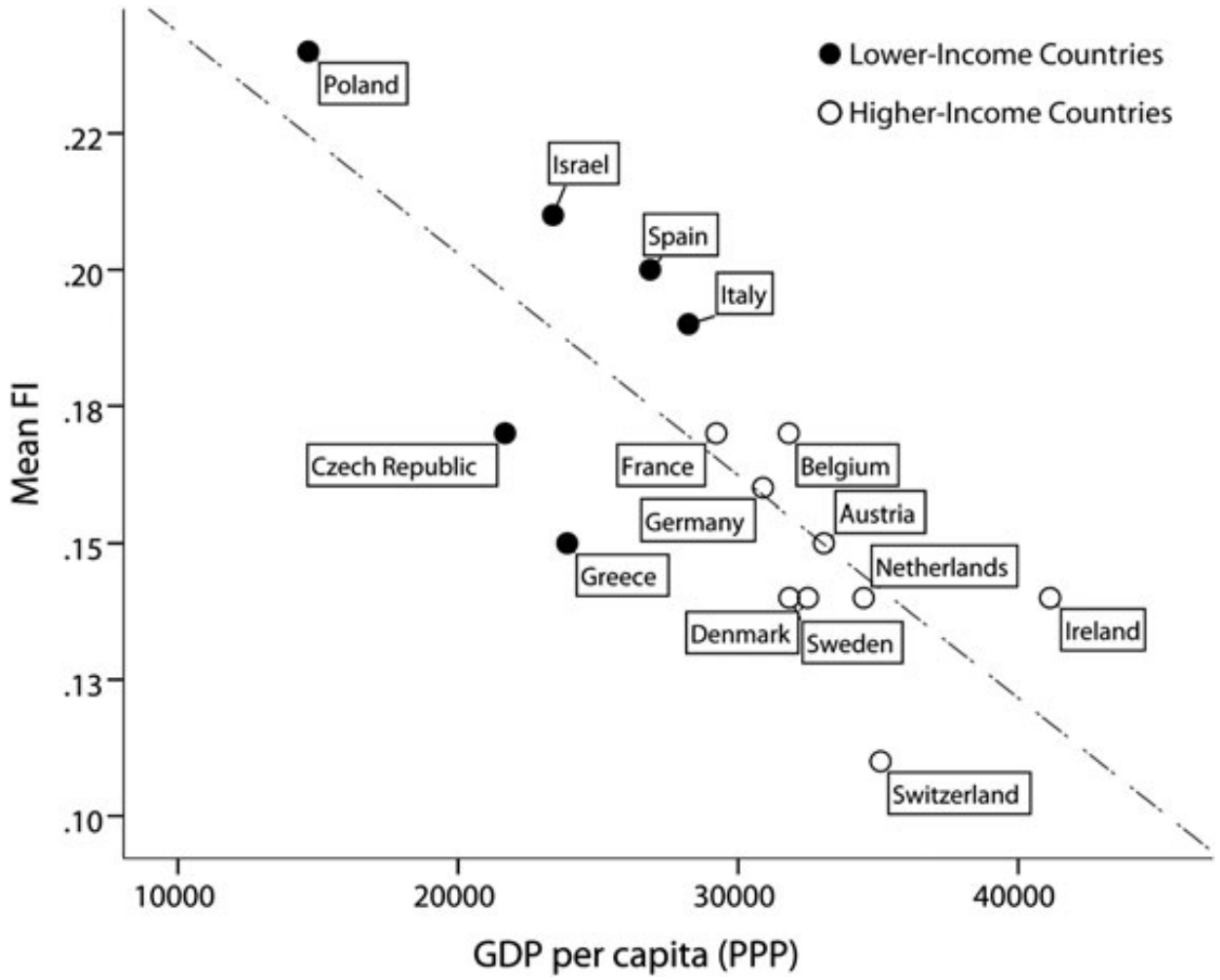
Country	Population	n	Frailty Prevalence
Brazil	≥65 years	735	17-23%
Mexico	≥70 years	838	15%
China	≥65 years	4000	5%
Russia	≥65 years	611	21%

- Heterogeneous
  - Age distributions
  - Approach to measuring frailty

Nguyen *et al. J Nutr Health Aging* 2015; 19: 941

Frailty prevalence and country income in Europe

- SHARE database
  - Non-institutionalized adults ≥50 years
- Cumulative deficit index



Theou *et al. Age Ageing* 2013; 42: 614

What are the major knowledge gaps when it comes to frailty?

- To what extent is frailty a global problem?
- Does frailty begin prior to ”older” age?
- *How* does frailty lead to premature death?
  - Does frailty lead to disease?
  - Does frailty lead to death independently of disease?

Frailty in middle age

Study	Frailty index	Age	Frailty prevalence	
Blodgett	Cumulative deficit Abbreviated phenotype	≥50 years (mean 63 years)	Abbreviated phenotype • Pre-frail: 27% • Frail: 4%	Cumulative deficit • ”vulnerable”: 38% • Frail: 34%
Rockwood	Cumulative deficit	>20 years	• Age 20-44 years: mean ± SD FI 0.08 ± 0.07 • Age 45-64 years: mean ± SD FI 0.16 ± 0.11	

Blodgett *et al. Arch Gerontol Geriatr* 2015; 60: 464
Rockwood *et al. Sci Rep* 2017; 7: 43068

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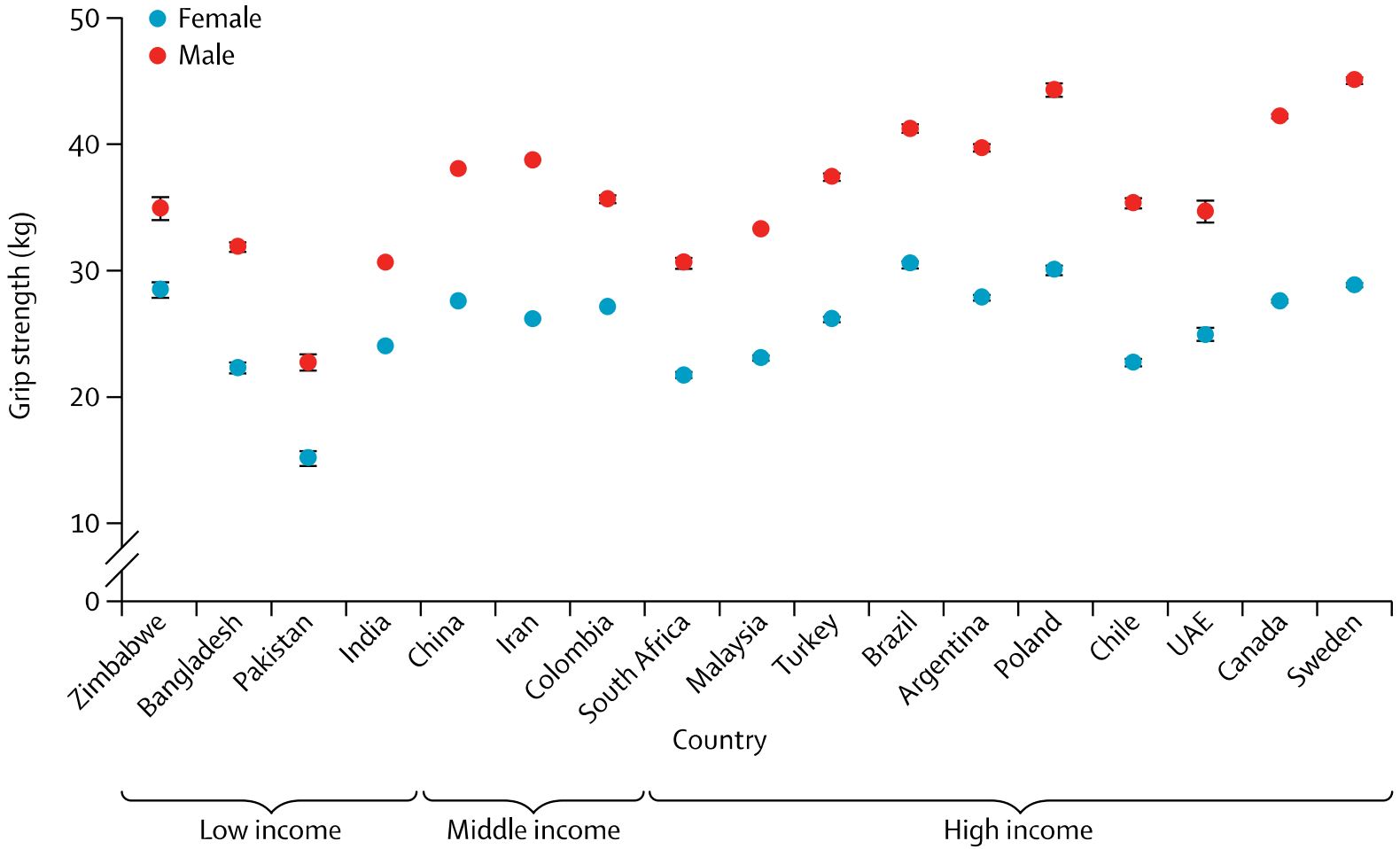
PURE Study

- Nearly 200,000 adults from 26 high-, middle-, and low-income countries
- 35-70 years old (median 50 years)
- 59% women
- Followed for median 8.8 years

Grip strength in different PURE countries



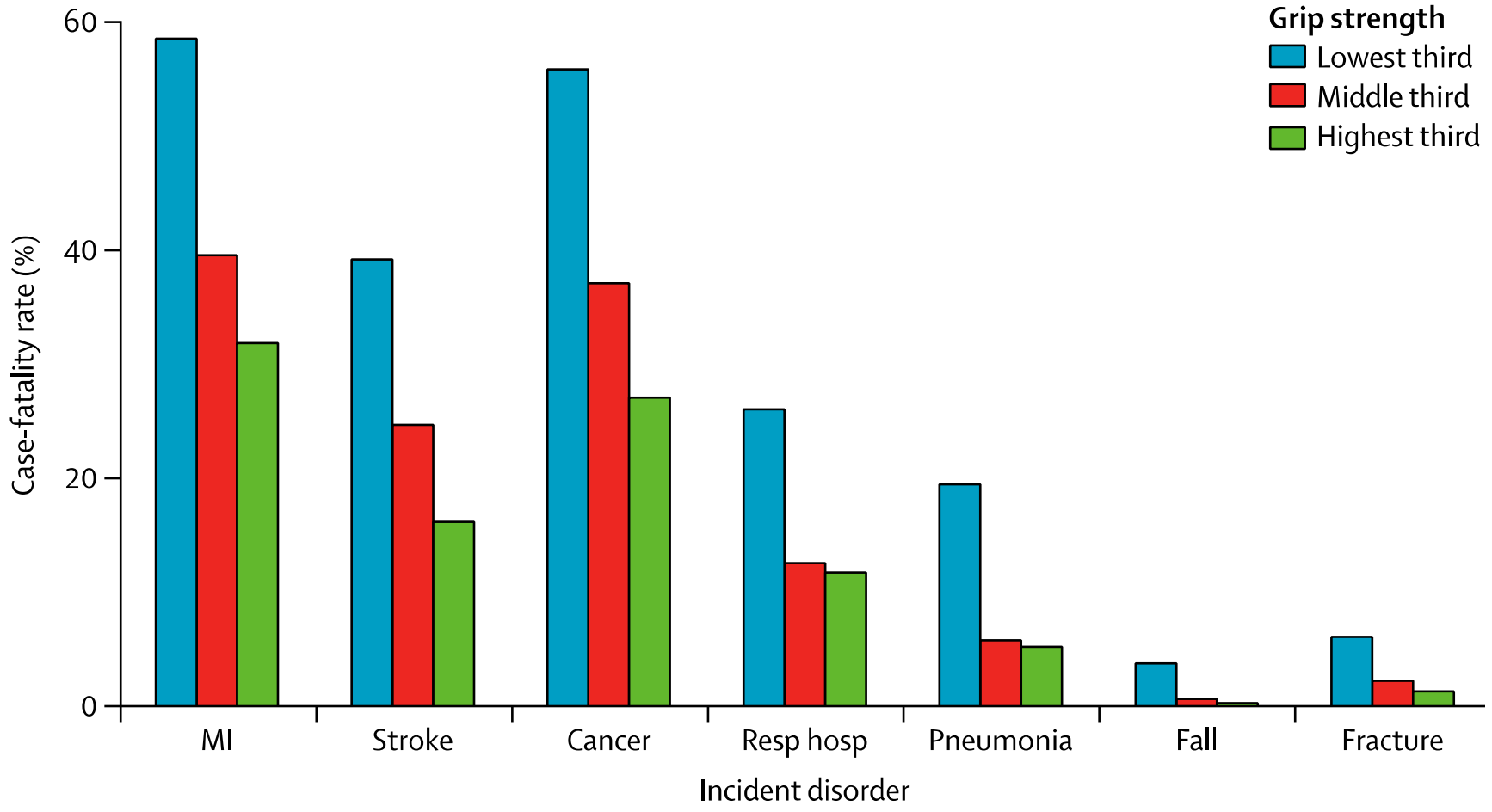
Leong *et al. Lancet* 2015; 386: 266

Grip strength and mortality

Outcome	Adjusted HR (95% CI) per 5kg reduction in grip strength
Death	1.16 (1.13-1.20)
Non-cardiovascular death	1.17 (1.11-1.24)
Cardiovascular death	1.17 (1.12-1.21)

Leong *et al. Lancet* 2015; 386: 266

Incident disease case-fatality rates



Leong *et al. Lancet* 2015; 386: 266

PURE Evaluation of Frailty

- Cumulative deficit index
  - 47 characteristics/deficits
  - >0.1 to ≤0.21 = pre-frail
  - >0.21 = frail
- Phenotype
  - Grip strength
  - Unintended weight loss (>3kg in last 6 months)
  - Physical activity (IPAQ)
  - 1 = pre-frail
  - ≥2 = frail

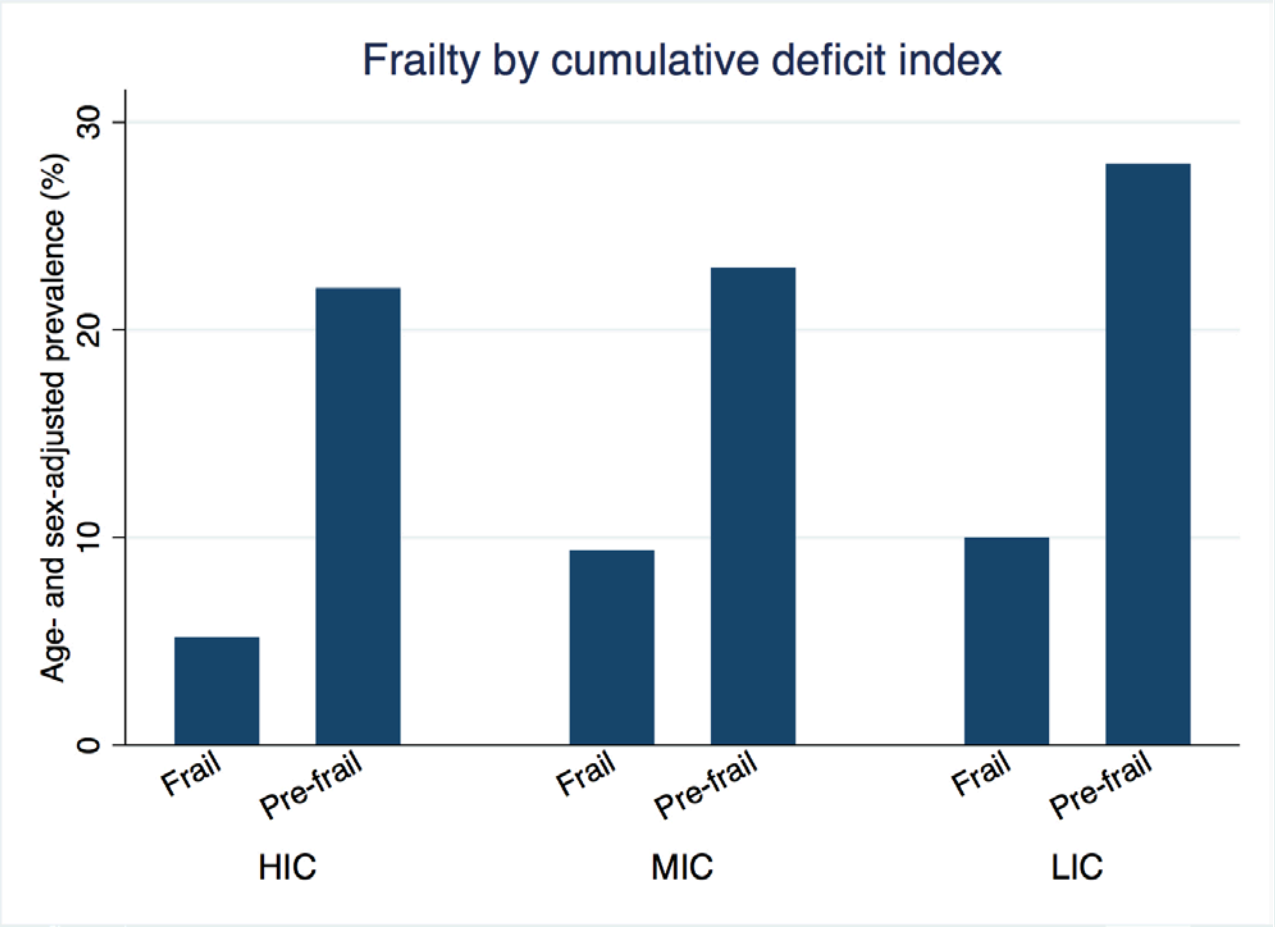
Characteristics of pre-frail and frail

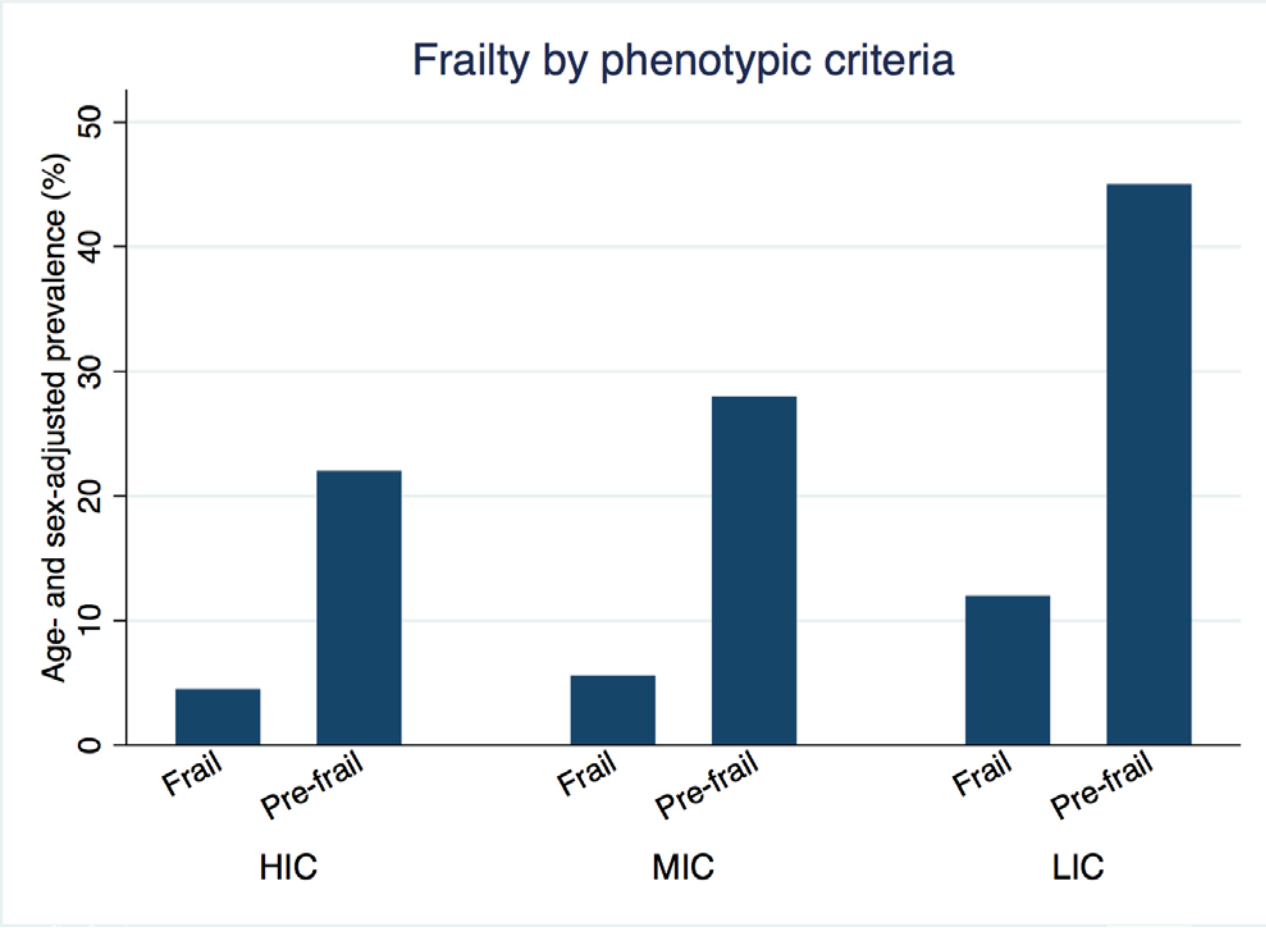
	Frailty phenotype N=132,797			Frailty by cumulative deficit index N=195,800		
	Non-Frail 65%	Pre-Frail 29%	Frail 6%	Non-Frail 67%	Pre-Frail 24%	Frail 9%
Men (100%) Women (100%)	65% 63%	29% 30%	6% 7%	71% 64%	22% 26%	7% 10%
Median age	50 (42-57)	52 (43-60)	55 (47-64)	49 (42-57)	54 (46-61)	56 (48-62)
Education Primary Secondary Uni/college	 56% 67% 72%	 34% 28% 24%	 10% 5% 4%	 61% 76% 75%	 27% 19% 20%	 12% 5% 5%

Characteristics of pre-frail and frail

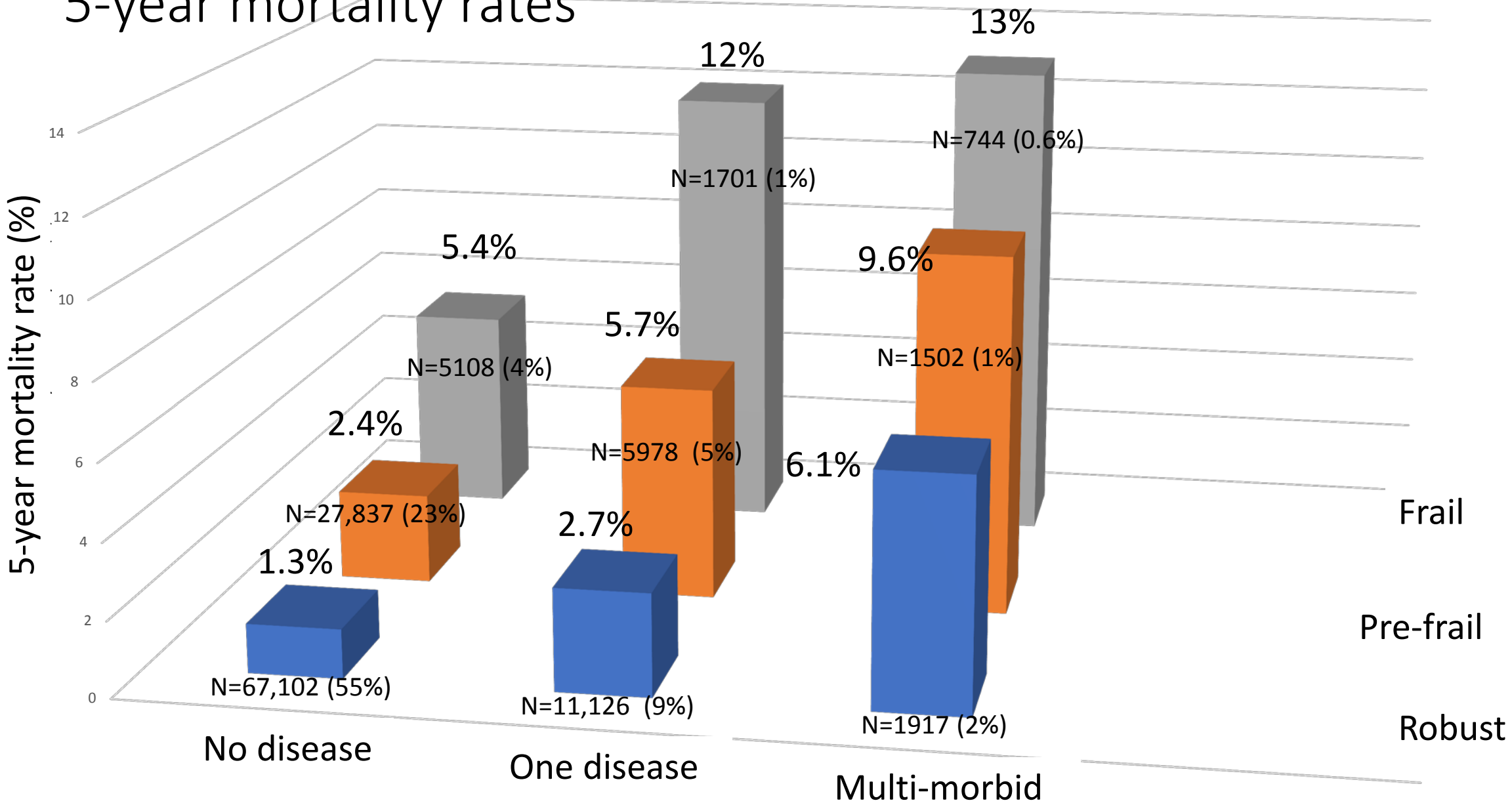
	Frailty phenotype N=132,797			Frailty by cumulative deficit index N=195,800		
	Non-Frail 65%	Pre-Frail 29%	Frail 6%	Non-Frail 67%	Pre-Frail 24%	Frail 9%
Tobacco						
Former	71%	24%	5%	56%	31%	13%
Current	65%	29%	6%	65%	25%	10%
Never	62%	31%	7%	70%	22%	8%
Alcohol						
Former	62%	31%	7%	50%	33%	17%
Current	75%	22%	3%	64%	27%	9%
Never	59%	33%	8%	71%	22%	7%

Frailty patterns by country income



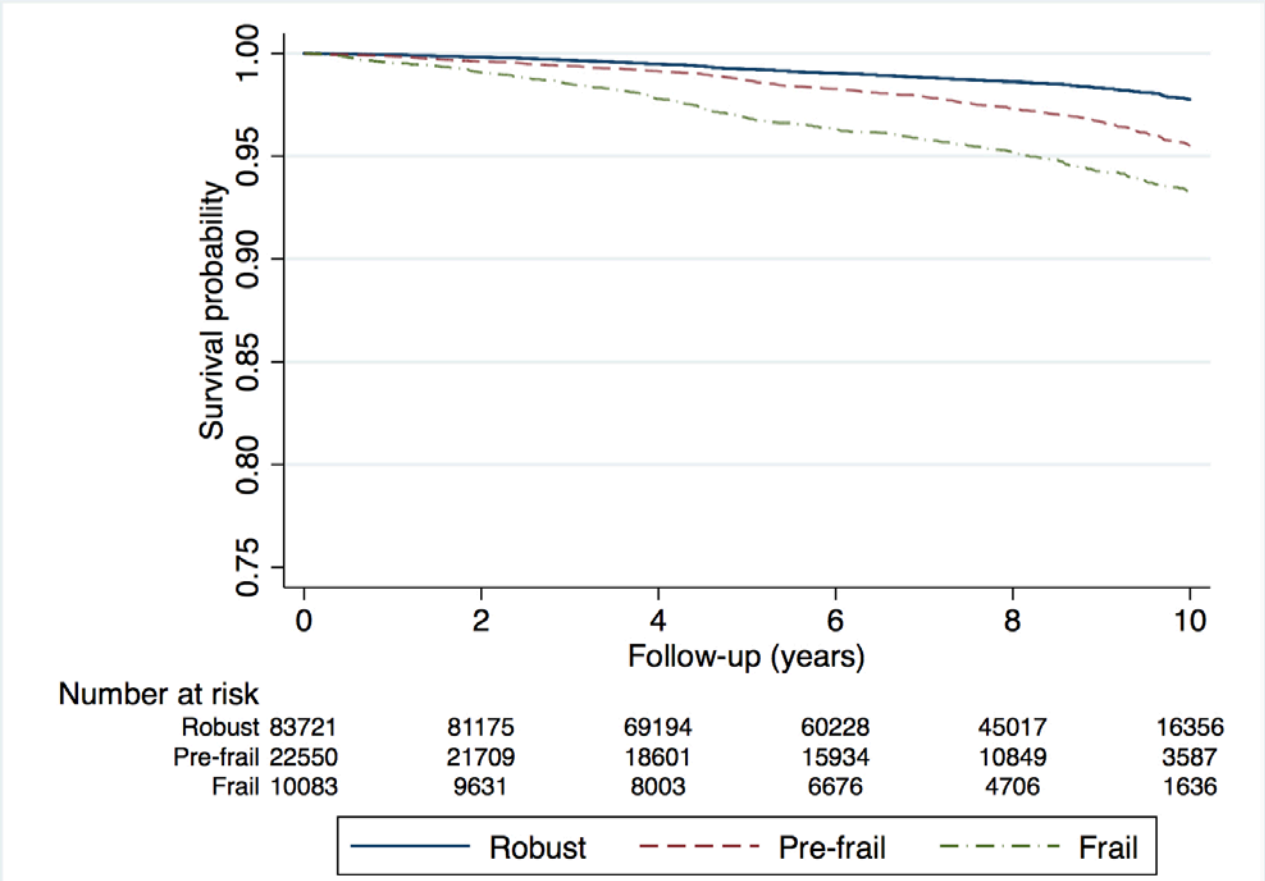


5-year mortality rates

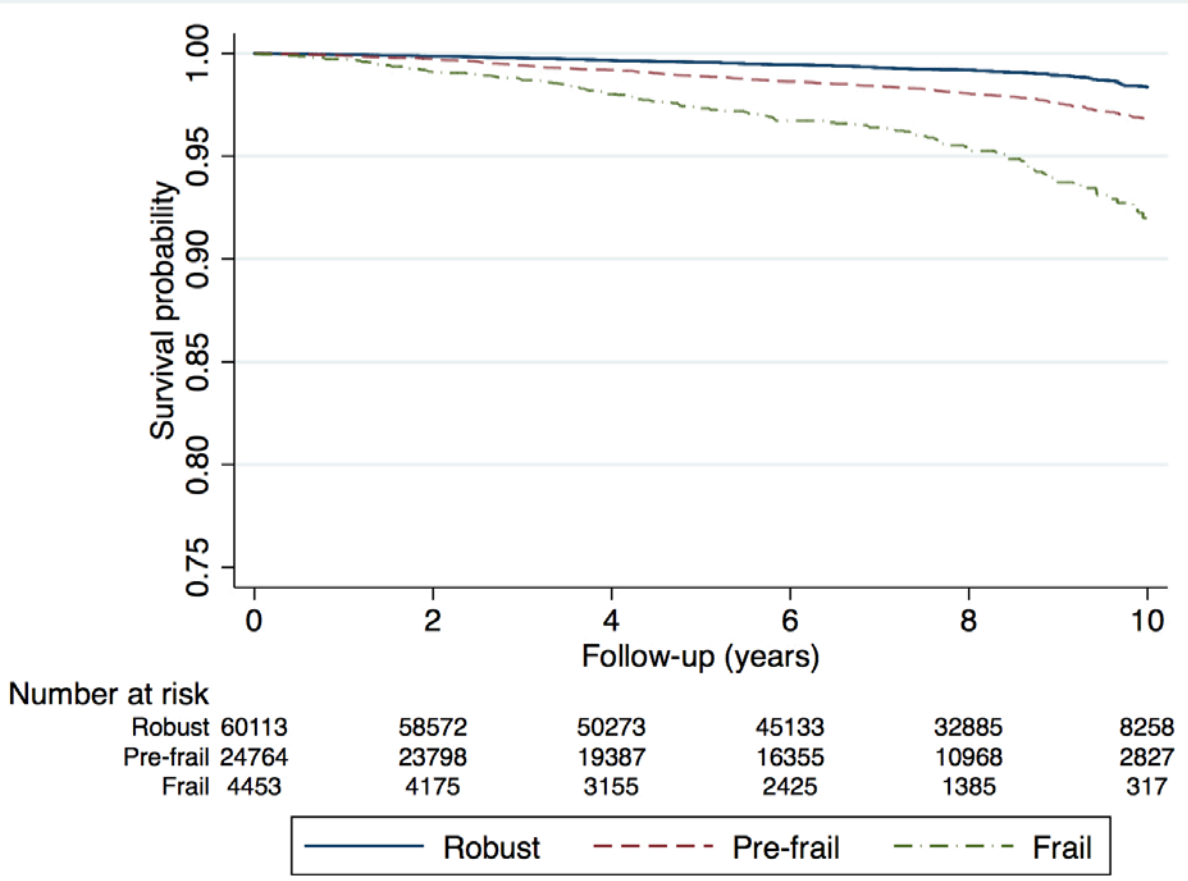


Frailty and mortality in those with no baseline or incident disease

Cumulative deficit index



Phenotype



Excluding those with baseline chronic disease

Outcome	Non-frail phenotype	Pre-frail phenotype	Frail phenotype
Death	1	1.25 (1.15-1.36)	1.87 (1.65-2.13)
Cardiovascular death	1	1.29 (1.10-1.51)	1.69 (1.33-2.15)
Non-cardiovascular death	1	1.25 (1.13-1.38)	1.99 (1.71-2.31)

Adjusted for country income, age, sex, education, tobacco and alcohol use, daily caloric intake, baseline diabetes, cardiovascular disease, and systolic blood pressure

Frailty phenotype does not directly cause disease

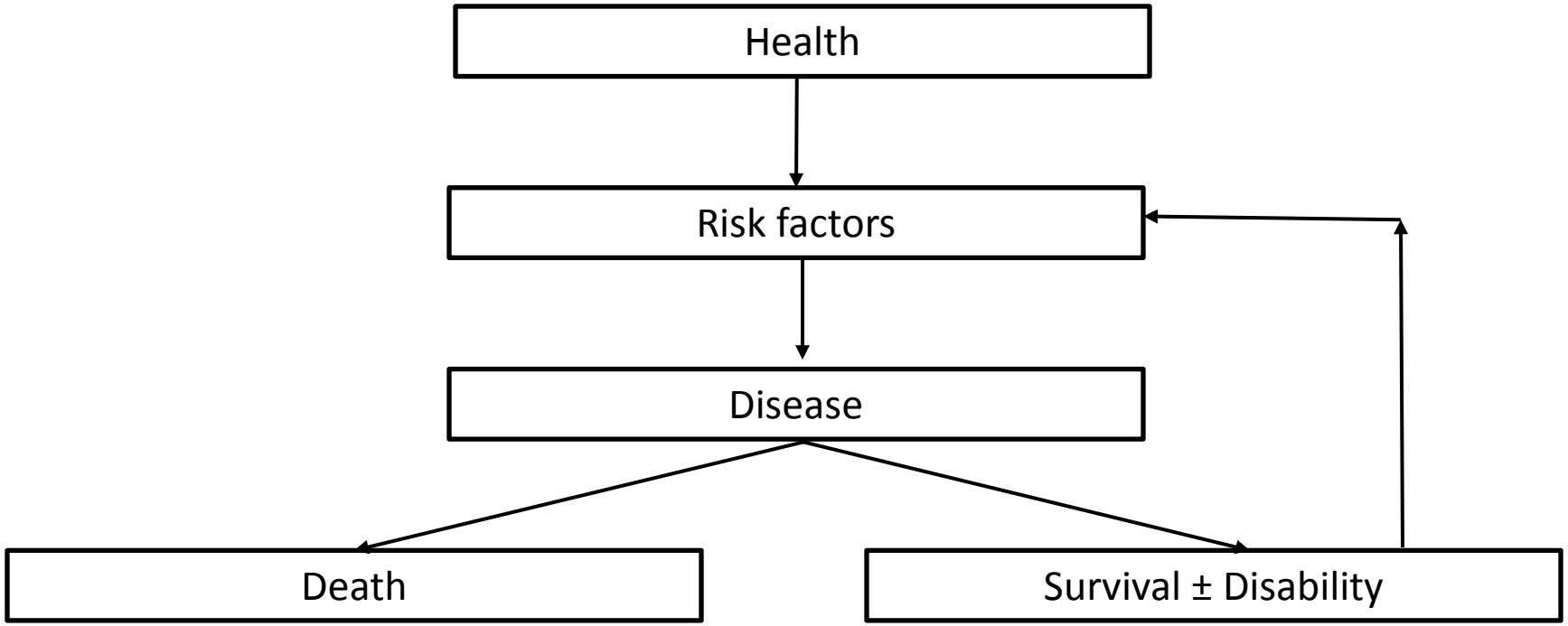
Incident disease	Pre-frailty		Frailty	
	Adjusted odds ratio*	95% confidence interval	Adjusted odds ratio*	95% confidence interval
Myocardial infarction	1·10	0·98-1·24	1·03	0·82-1·28
Stroke	1·12	1·00-1·25	1·09	0·89-1·34
Heart failure	1·08	0·84-1·40	1·28	0·83-1·97
Cancer	0·95	0·86-1·06	0·90	0·73-1·11
Pneumonia	1·12	0·97-1·30	1·26	0·94-1·69
COPD	1·15	0·98-1·34	1·25	0·93-1·69
Any incident disease	0·99	0·94-1·05	1·02	0·93-1·13

*adjusted for country income, age, sex, education, alcohol or tobacco use, and dietary caloric intake

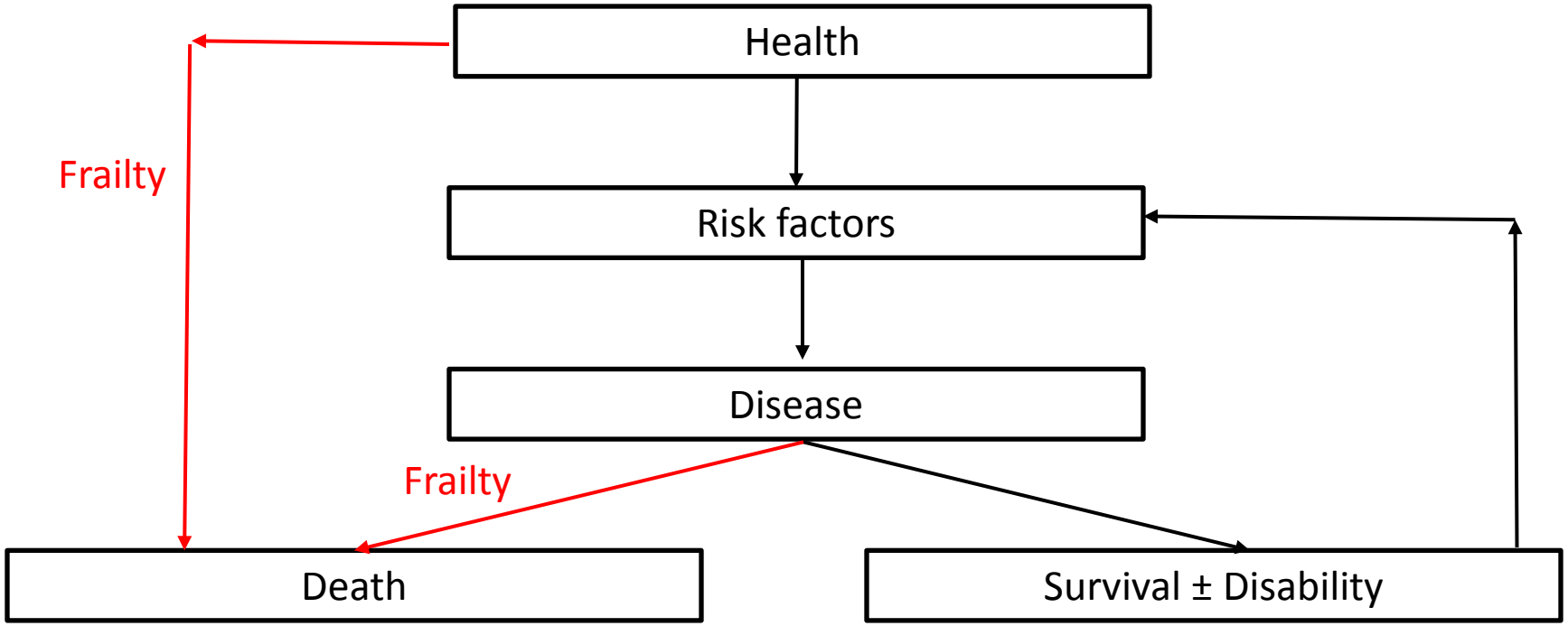
Case-fatality rates by frailty phenotype

Incident condition	Non-frail	Pre-frail	Frail
Myocardial infarction	24%	32%	44%
Stroke	17%	25%	41%
Heart failure	25%	37%	51%
Cancer	33%	47%	62%
Pneumonia	7%	16%	35%
Chronic obstructive pulmonary disease	5%	8%	14%
Any hospitalization	7%	13%	23%

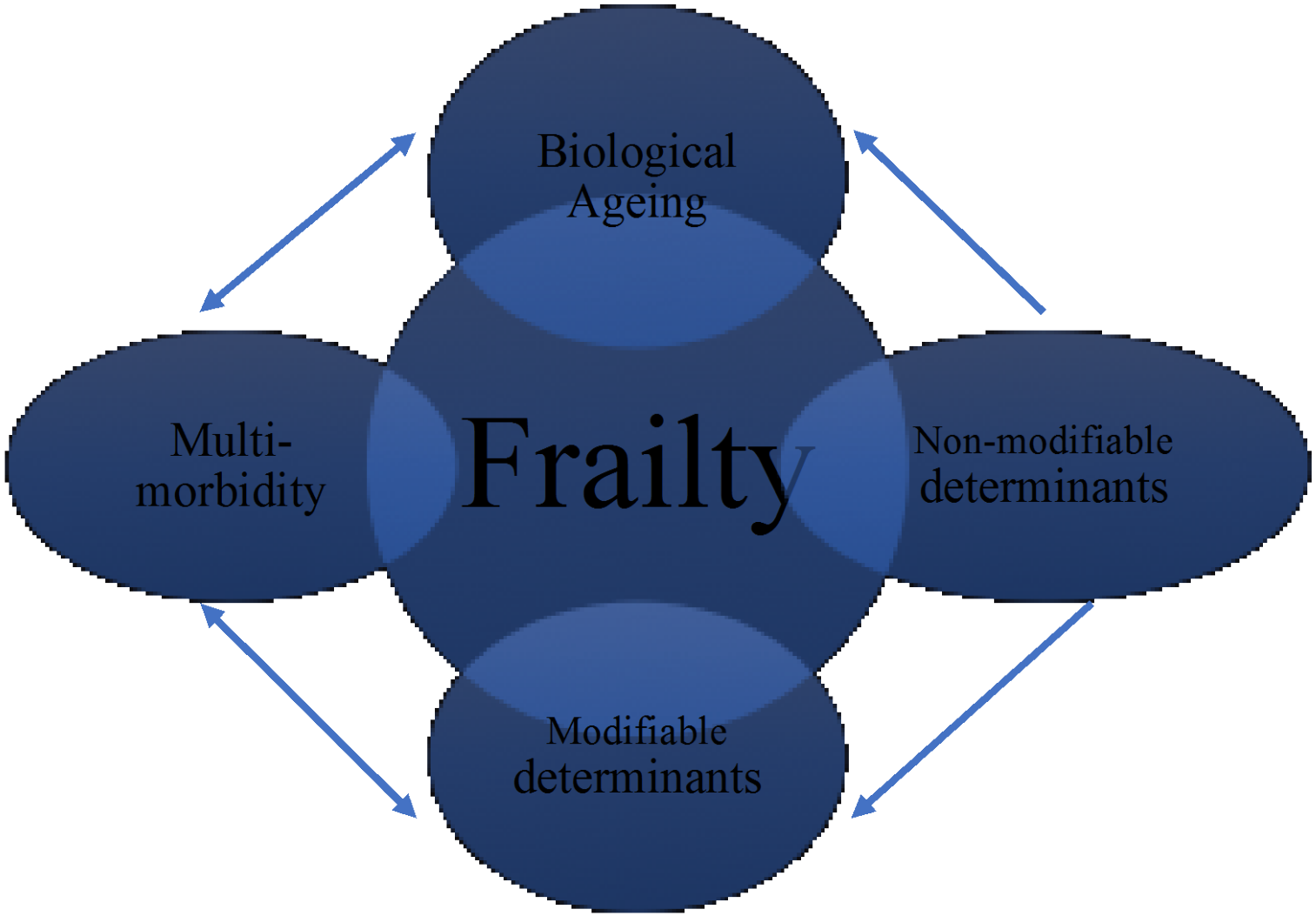
The classic model of death



Conclusion


Health
Risk factors
Disease
Death
Survival ± Disability
Frailty
Frailty

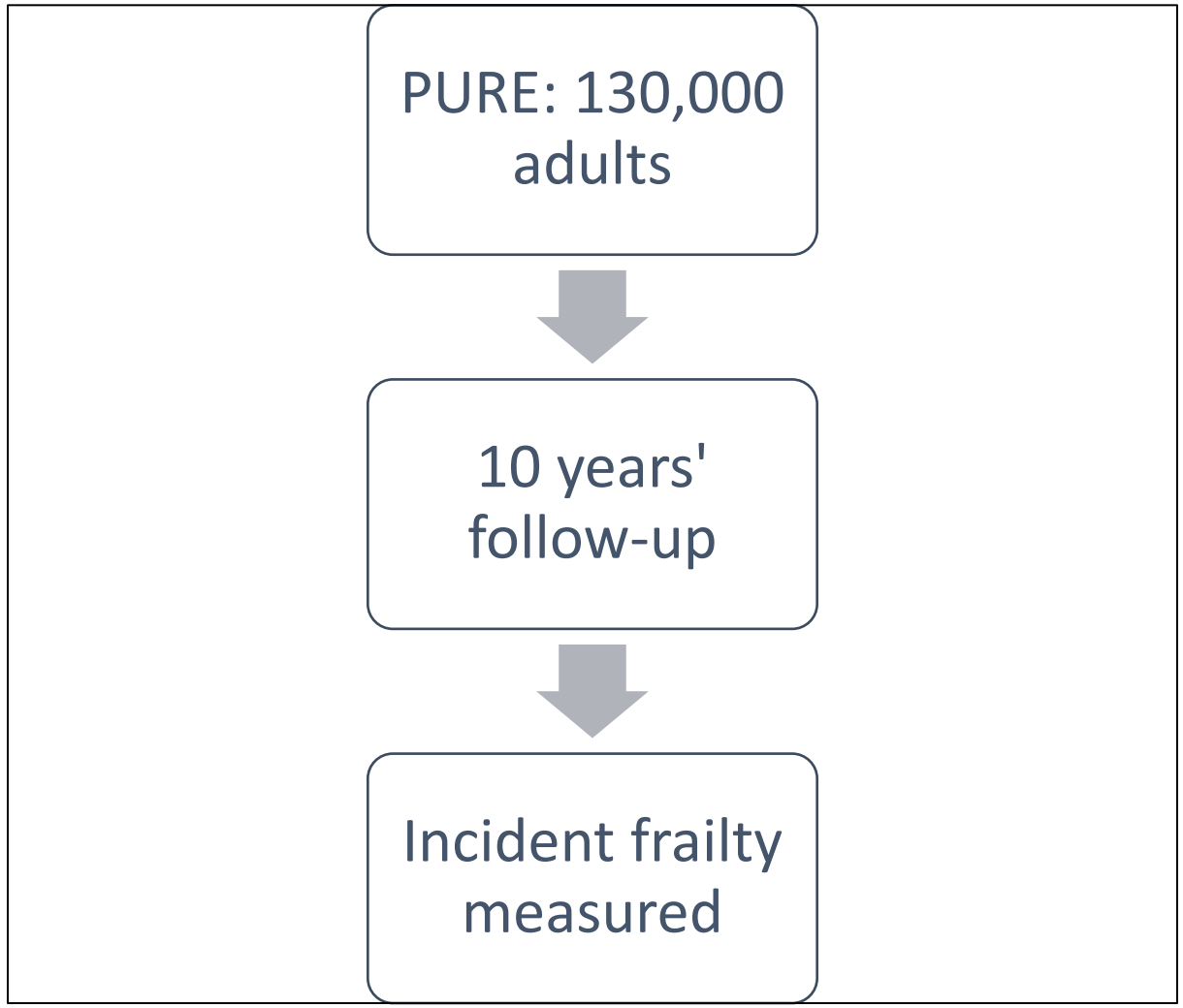
A Model of Frailty

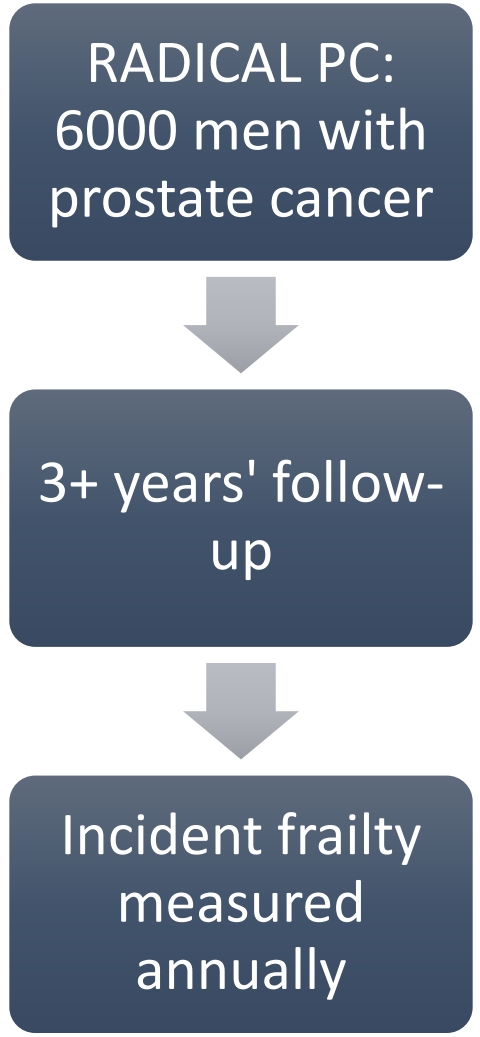


Potential Determinants of Frailty

Biologic Ageing	Modifiable Determinants	Diseases & Multi-morbidity	Non-modifiable Determinants
Telomere shortening Somatic mutations Mitochondrial DNA mutations	Individual risk factors: diet, physical activity Ecological exposures: air pollution, education	Chronic disease polypharmacy	Sex Ethnicity

Identifying the causes of frailty





Next Steps

Blood biomarkers

Behavioural factors

Frailty

Genetic markers

Non-modifiables

Categories of biomarker

Category	Example
Immunological	T-cell phenotype
Metabolic	Lipid profiles Uric acid concentration Vitamin D concentration
Inflammatory	CRP IL-6
Endocrine	Testosterone Thyroid hormone Glycation end-products
Oxidative stress	Glutuathione Malondialedhyde

Advances in biomarker analytics

- Multiplex platforms
- Hundreds of biomarkers measurable with very small quantities of plasma
- Patterns of biomarkers (rather than any single biomarker) may be important
- Artificial intelligence may enable understanding

Summary

Frailty and pre-frailty

- Are common, especially in poorer settings and countries
- Can be clearly identified from middle age
- Lead to death by
  - Increasing susceptibility to an incident illness
  - Independently of disease

Conclusion

- Reducing frailty may represent an under-exploited avenue for reducing mortality (and likely disability) that complements existing efforts to prevent and treat disease

UPCOMING CLSA WEBINARS

“Enriching the CLSA with environmental exposure data: The Canadian Urban Environmental Health Research Consortium (CANUE)”

Dany Doiron, Jeff Brook, Eleanor Setton

October 23, 2018 | 12 p.m. EST

Register: bit.ly/clsawebinars