Frailty
An Emerging Clinical and Research Paradigm?

Howard Bergman, MD

The Dr. Joseph Kaufmann Professor and Director
Division of Geriatric Medicine, McGill University

Co-Director: Solidage Research Group

Director
Quebec Research Network in Ageing
Fonds de Recherche en Santé du Québec

Chair
Advisory Board, Institute of Aging
Canadian Institutes of Health Research

SOLIDAGE

www.solidage.ca

Groupe de recherche Université de Montréal/McGill sur les services intégrés pour les personnes âgées

McGill/Université de Montréal Research Group on Integrated Services for Older Persons

Version 09.07

Lausanne

Hôpital général juif
Sir Mortimer B. Davis
Jewish General Hospital

Centre d'épidémiologie clinique et de recherche en santé publique, Institut Lady Davis
Centre for Clinical Epidemiology and Community Studies, Lady Davis Institute

Université de Montréal

Département d'administration de la santé
Groupe de recherche Interdisciplinaire en santé (GRIS)

McGill University

The Dr. Joseph Kaufmann Chair in Geriatric Medicine
La Chaire Dr Joseph Kaufman en gériatrie

Centre de recherche

Institut universitaire de gériatrie de Montréal

Acknowledgements

- Canadian Initiative on Frailty and Aging
- 2nd International working meeting on Frailty and Aging (Montreal March 2006)
  - Building on 1st International meeting (Lausanne 2003) and AGS/NIA meeting (Baltimore 2004)
  - Organizing Committee: H Bergman, C Wolfson, L Ferrucci, J Guralnik, D Hogan
  - Participants
    - » geriatric medicine, epidemiology, public health, biostatistics, biology, neurology, oncology and sociology
    - » Canada, USA, Switzerland, Israel, Italy, Mexico, Netherlands, Germany, Japan, UK, Spain, France, Singapore
- Solidage (McGill/UdeM)-CIHR funded research team on frailty and aging

2nd International Working Meeting on Frailty and Aging Montreal March 2006

Objectives

- advance our understanding of frailty through a multidisciplinary perspective;
- identify a series of cogent research questions regarding frailty;
- examine methodological approaches with the goal of developing population and clinical studies on frailty and aging;
- establish mechanisms for collaboration among investigators.

- Frailty, an Emerging Research and Clinical Paradigm: Issues and Controversies. Journal of Gerontology: Medical Sciences 2007 (In Press)
  - Howard Bergman, Luigi Ferrucci, Jack Guralnik, David Hogan, Silvia Hummel, Sathya Karunananthan, Christina Wolfson

Frailty: an emerging concept
Comments on a Case

- Complex things fail in complex ways
- System breakdown leading to catastrophic failure
- Made vulnerable by multiple, interacting factors
- If had been “healthy” the insults would not have caused sufficient damage leading to failure; predisposed by ageing

Columbia Shuttle

Mrs. D.

Mrs. D.

Mrs. D. is an 82 year old widow(x15 years), 3 adult children and an active social life. Her PMH includes mild MI (3 years ago), osteoporosis and osteoarthritis. Her cognition is normal and she is compliant with medications. She walks with a cane in her home but needs a walker outside. She is independent in all ADL and in IADL but needs help for transportation which she organises herself

Mrs. D.

Mrs. D. is a 71 year old widow (x 12 years) with 4 adult children. PMH includes diabetes and osteoarthritis. She lives alone and tends to be isolated with some mildly depressive episodes. Her nutritional intake is poor. She walks without aids but seems to have slowed down lately. Her cognition is normal. She is compliant with her medication. She is independent in all ADL and IADL

- Is Mrs. D. frail
- What is frailty
- What are the components of frailty

So What????

- Can her vulnerability be identified in the clinical setting
- Can the potential adverse outcomes, in particular disability, be prevented or delayed
- Is frailty a useful concept

Frailty: an Emerging Concept

- Survey 1999 Annual Meeting of the Canadian Association on Gerontology
  - 356 respondents – 2/3 felt it was a clinically useful concept
  - a state of risk or vulnerability; a precarious balance between demands and capacity to cope; and impending or current disability

Kaethler Y et al. J Can Geriatrics 2003

- Survey of 62 geriatricians
  - most felt that disability and frailty differed.
  - more than half cited as features of frailty: undernutrition, dependence, prolonged bed rest, pressure ulcers, gait disorders, generalized weakness, extreme old age, weight loss, anorexia, fear of falling, dementia, hip fracture, delirium, confusion, going outdoors infrequently, and polypharmacy.

Fried and Williamson

- Focus groups of older patients and their caregivers:
  - Emphasised emotional and social domains of frailty, in addition to the physical domains.

Studenski 2004

Frailty: an Emerging Concept

- "frail elderly" has been a Medline MeSH term since 1991
- defined as "older adults or aged individuals who are lacking in general strength and are unusually susceptible to disease or to other infirmity"
- Medline search: 248 to 291 papers/ year (2000-2005)
- NY Times: 2002 and 2006

The Challenge of Defining Frailty

- Frailty is like pornography: Clinicians can’t define it but they recognize it when they see it.

an anonymous clinician

Frailty: a proposed research and clinical entity

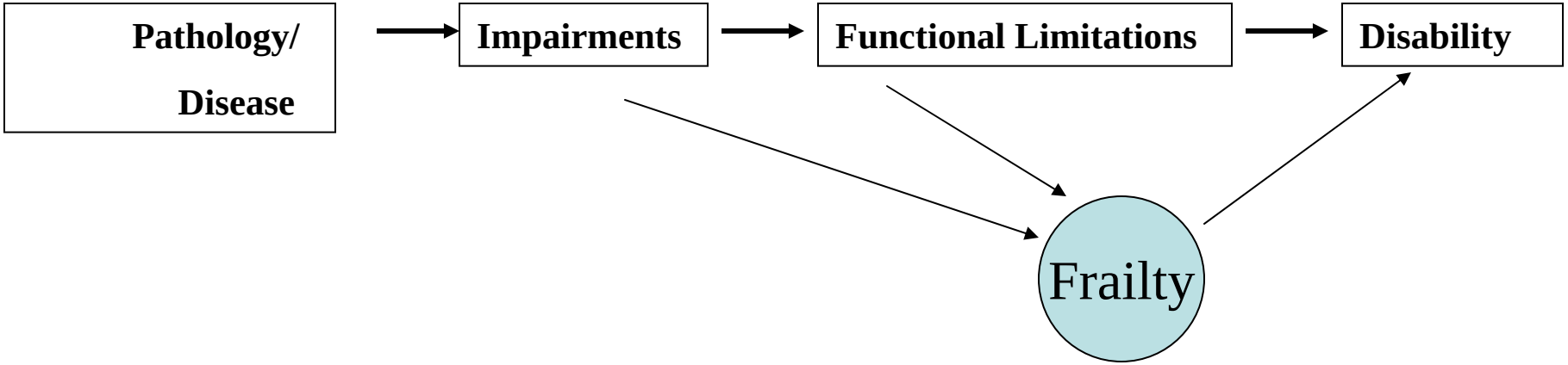
- Progressively dissociated from disability
- Models
  - Demographic and mathematical
  - Ageing
  - Genetic
  - Primary pathways
  - Concurrent dysfunction of multiple biological systems
  - Combined bio-medical/psychosocial
- 30 criteria for identifying frailty or predicting frailty

Hogan DB, et al. Aging Clin Exp Research. 2003

General Agreement

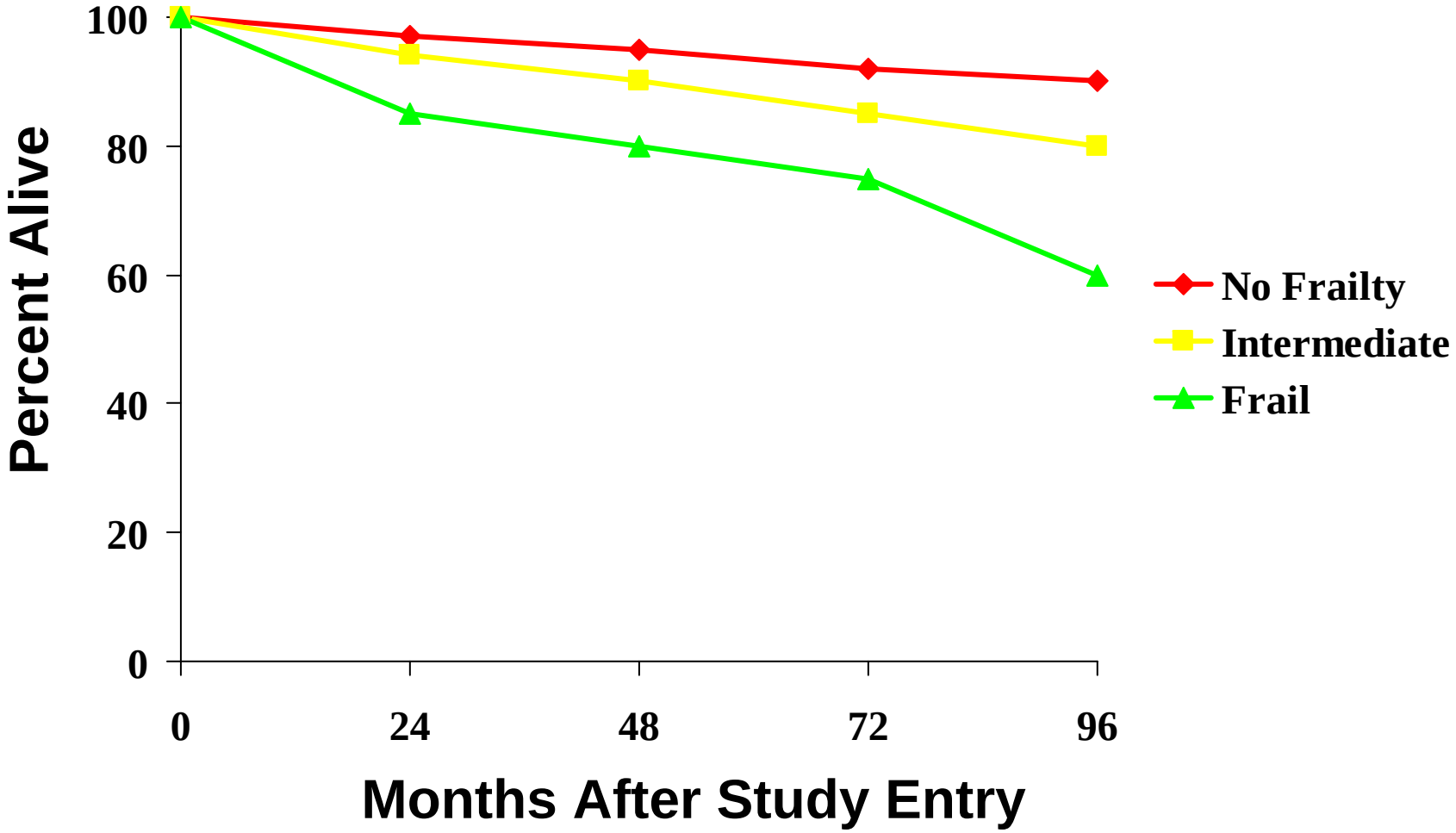
- Core feature of frailty is increased vulnerability to stressors due to impairments in multiple, inter-related systems that lead to decline in homeostatic "reserve" and resiliency
- The main consequence is an increased risk for multiple adverse health-related outcomes
  - disability, morbidity, falls, hospitalisation, institutionalisation, death
- a syndrome encountered in older persons with diverse predisposing, precipitating, enabling and reinforcing factors
- Frailty and disability: while related and with overlap, are distinct concepts

WHO/IOM Pathway to Disability



Survival According to Frailty Status

Cardiovascular Health Study



Fried et al, J. Gerontology Med Sci, 2001

Working Approach

Characteristic clustering of:

- Physiological abnormalities
  - activation of the immune system, neuroendocrine dysregulation, sarcopenia,
- Cognitive and physical findings
  - impaired cognition, slow gait speed, reduced grip strength, documented weight loss
- Symptoms
  - anorexia, depressed mood, fatigue
- Other features
  - advanced age, personality characteristics, inactivity, isolation

Fried LP et al. J Gerontol: Med Sci 2001
Rockwood K et al, Drugs Aging 2000
Studenski S, et al. J Am Geriatr Soc 2004

Working Approach

- Domains
  - Nutrition
  - Mobility
  - Activity
  - Strength
  - Endurance
  - Cognition
  - Mood
- Balance between assets and deficits will determine the consequences for an individual; dynamic nature
  - adaptability, physical environment & social resources are important determinants of the impact of frailty.

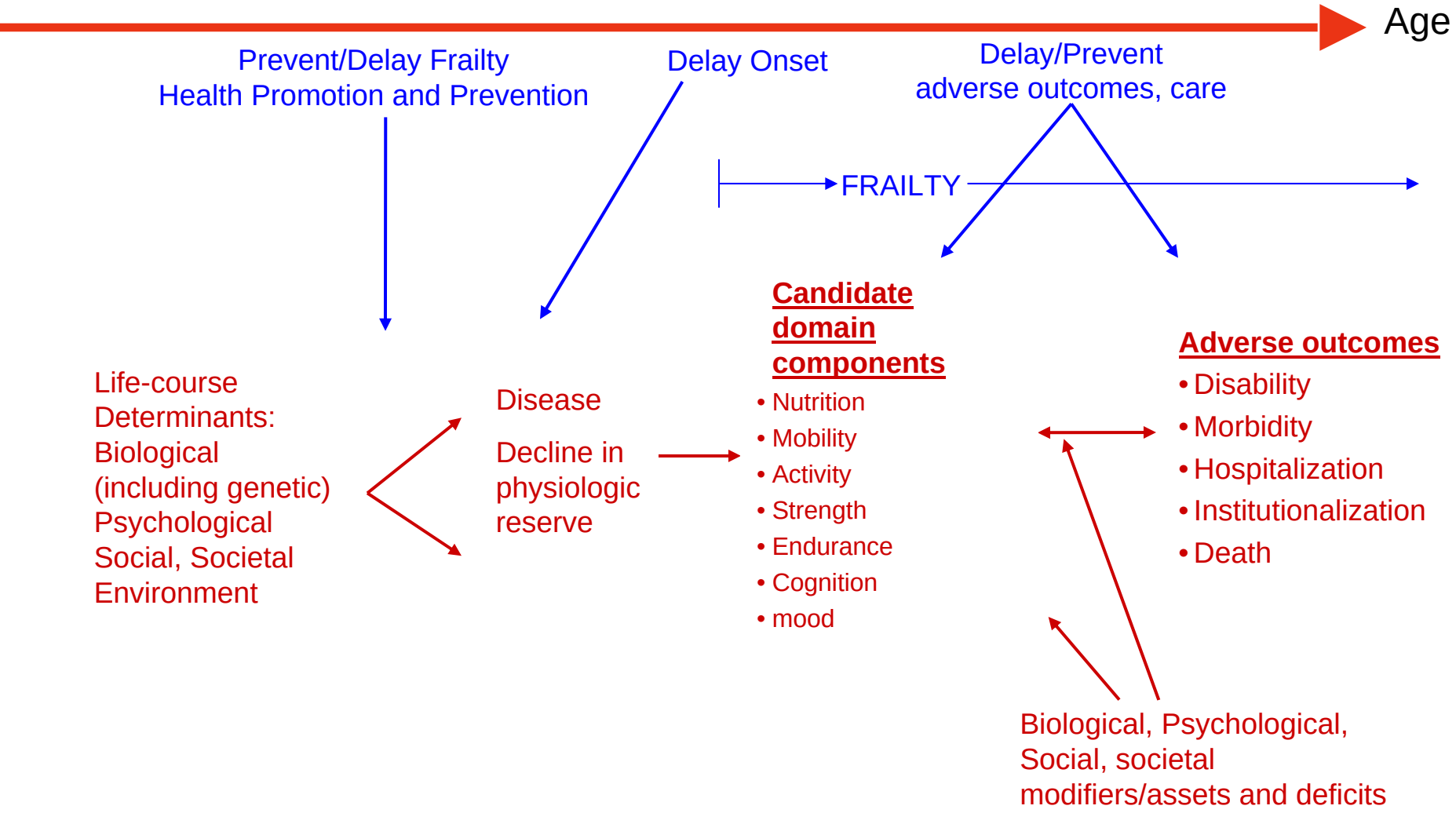
Lebel P et al 1999

Studenski S, et al. J Am Geriatr Soc 2004

Bergman H et al. Gérontologie et société 2004 (English version available)

Frailty: a Complex Syndrome of Increased Vulnerability

A possible working framework



Frailty: a Complex Syndrome of Increased Vulnerability: a Complex Etiology

- An integrative approach that includes the biological, social, clinical (including cognitive), psychological and environmental determinants which interact across a person's lifespan and which may promote healthy ageing and either delay or promote the emergence of frailty
  - The contribution of early life factors jointly with later life factors to identify risk and protective processes
  - Integrate biological and social risk processes rather than draw false dichotomies

Adapted from: Ben-Shlomo Y, Kuh D. Int J Epidemiol 2002

Examples of risk factors/markers across the life span

- Low birth weight associated with
  - ↓ grip strength 53 years later — Kuh D. Am J Epidemiol 2002
  - ↑ risk of diabetes and cardiovascular disease — Aboderin et al. WHO 2002
- Prenatal, prepubertal, pubertal growth associated with midlife grip strength — Kuh 2006
- Decreased grip strength in mid life
  - ↑ risk of functional decline and disability 25 years later — Rantanen T 1999
- Father's occupation/mother's education-physical functioning 50 years later — Guralnik 2006
- Risk factors for frailty
  - age; low education
  - 30 year cumulative predictors: heavy drinking, cigarette, physical inactivity, depression, poor perceived health, 2 or more chronic symptoms, 1 or more chronic conditions, social isolation

Strawbridge. J of Gerontol: Soc Sci 1998

Frailty, an Emerging Research and Clinical Paradigm: Issues and Controversies

- what is the difference, if any, between frailty and aging?
- What is its relationship with chronic disease?
- Is frailty a syndrome or a series of age-related impairments that predict adverse outcomes?
- What are the critical domains its operational definition?
- Is frailty a useful concept?

Bergman H, Ferrucci, L, Guralnik J, Hogan D, Hummel S, Karunananthan S, Wolfson C
J Gerontol: Med Sci: 2007

Issues/Controversies
Frailty and Aging

- Many of the attributes of frailty also apply to aging
- Some degree of functional impairment/vulnerability inevitable with very old age

Deiana L et al. Aging 1999; Gondo Y et al. J of Gerontol: Med Sci 2006

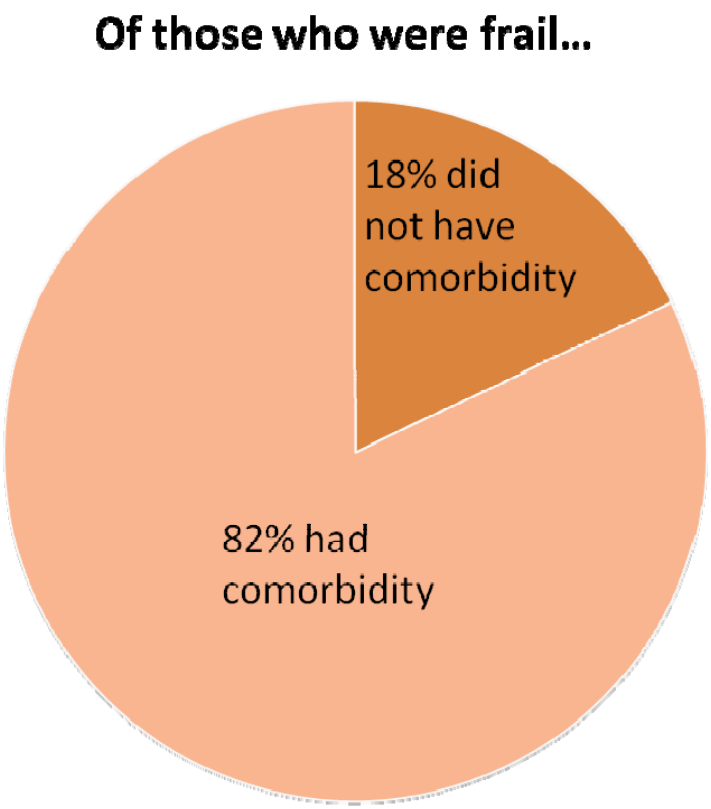
- An arbitrarily defined point on a continuum of increased vulnerability with age
- Inevitable part of the aging process/flip side of healthy aging

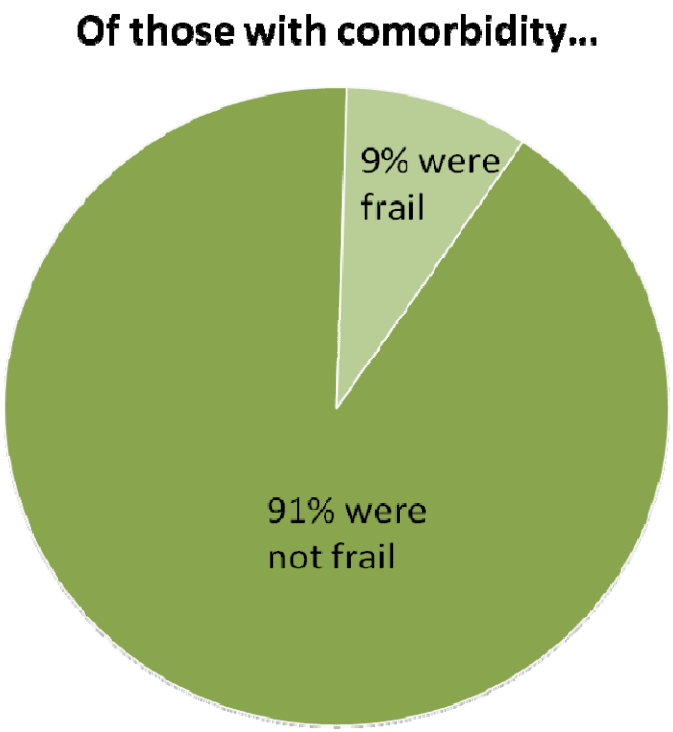
- Nevertheless, the conceptualization of frailty may help in understanding the heterogeneity of functional decline observed with chronological aging.
  - Chronological age alone is only a rough proxy of a person's vulnerability to adverse outcomes.
  - Some people appear to be frail (however defined) at age 70, while others only reach this state in their 90s.

Issues/Controversies
Frailty and Chronic Disease

- A complex relationship-almost all frail persons have chronic disease but most persons with chronic disease are not frail
- Increasing prevalence of frailty with increasing chronic disease
- Frailty is a manifestation of clinical and undiagnosed chronic disease, a secondary condition rather than an underlying state?
  - primary vs secondary frailty?

frailty and comorbidity





Wong, Weiss, Sauriol, Karunananthan, Quail , Wolfson, Bergman. Frailty and its association with disability and comorbidity in a community dwelling sample of seniors in Montreal. Manuscript in preparation

The Frailty Phenotype

- A clinical syndrome with specific manifestations linked to an underlying biologic pathway
- neuroendocrine and immune dysfunction, sarcopenia
- Grip strength; exhaustion/fatigue; less physically active; slow gait; unintentional weight loss

  Cardiovascular Health Study
- Prevalence 6.9%, 4 year incidence 7.2%
- Predictive of falls, mobility/ functional decline, hospitalization, and death (within 3 years); adjusted HRs 1.3-2.2

Fried LP et al. J Gerontol: Med Sci 2001

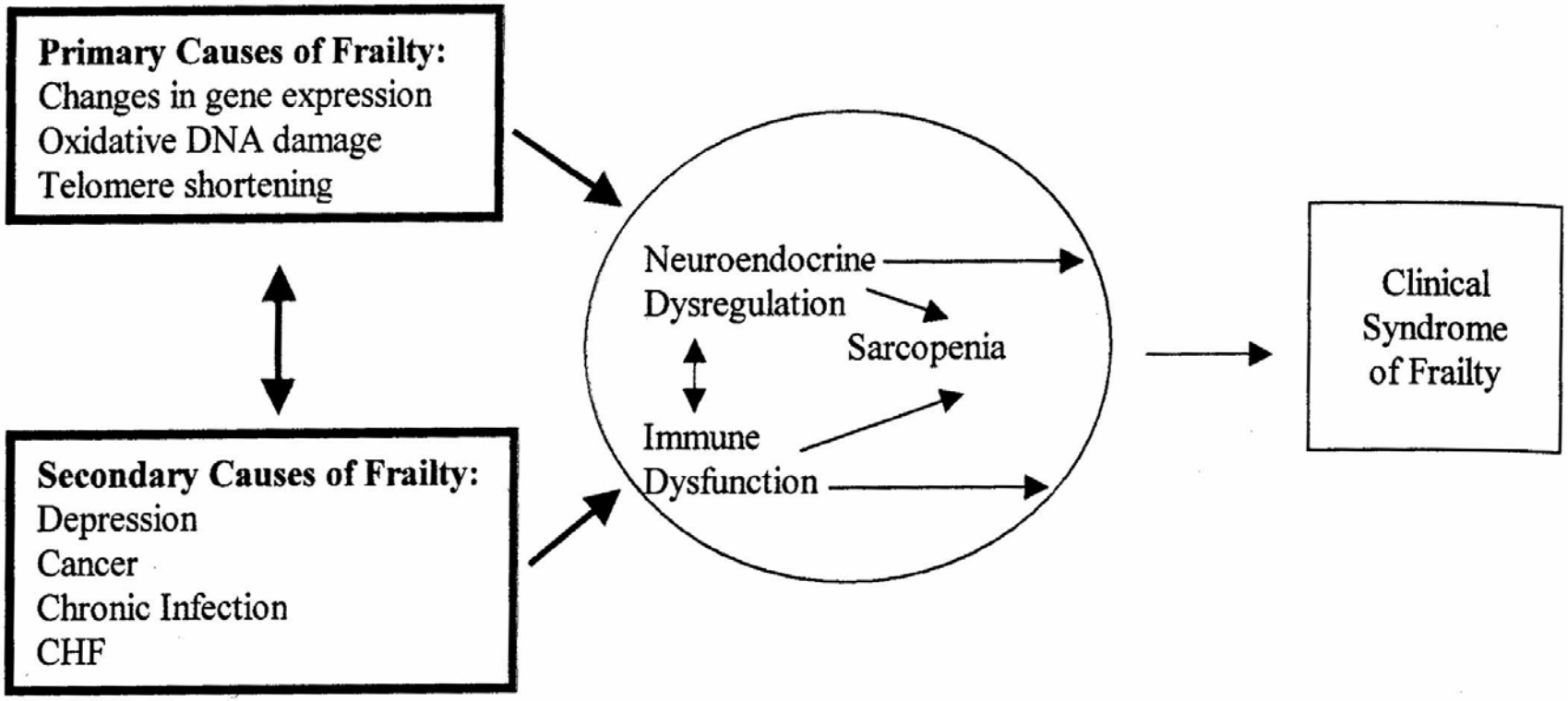


Figure 116-9 Hypothetical causal pathway of frailty focused on primary, age-related mechanisms, and secondary disease-related mechanisms. We hypothesize that both mechanisms can trigger the physiology of frailty, and that there is substantial interaction between primary and secondary mechanisms.

Fried 2003

Frailty Index

- Identified 40 self-reported variables representing symptoms, attitudes, illnesses, and function
- strongly correlated with mortality; exponential increase of frailty with age
- Based upon secondary analysis of the Canadian Study on Health and Aging

Mitnitski, Song, Rockwood, (2004). The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 59A(6), 627-632.

Spectrum of frailty models

Common features: Age-related vulnerability to stressors, clinically identifiable, multi-system impairment

Frailty Phenotype

- Hypothesis-driven
- Limited number of components linked to defined underlying biologic/physiologic pathway
- Dichotomous/threshold
- Separate from aging process
- Physiological/predictive
- Medical syndrome: aggregate of Sx and signs associated with morbid process constituting picture: Cushing

Frailty Index

- Risk factor approach
- Variable pathway and pathophysiology
- Unlimited number of deficits
- Continuous
- Predictive
- Geriatric syndrome: accumulated effects of impairments in multiple domains resulting in a particular adverse outcome:falls

Issues/Controversies
Lessons from the Metabolic Syndrome

- A multifaceted clinical entity produced by genetic, hormonal and lifestyle factors; not a disease; a clustering of metabolic abnormalities; risk greater than that of its individual components
- "The Metabolic Syndrome Still Lives"
  - "a powerful hypothesis that unifies the metabolic factors underlying the development of both arteriosclerotic cardiovascular disease and diabetes"
  - Risk factor clustering cannot be explained by chance alone
  - will facilitate the detection and clinical management of patients in spite of the variable clinical presentation.

Grundy SM. Clin Chem 2005

- " The Metabolic Syndrome: Requiescat in Pace"
  - does not bring much in the way of pathophysiologic understanding or clinical utility
  - lead to withholding treatment to those individuals who do not satisfy "three of the five arbitrarily chosen criteria; all risk factors should be treated

Reaven GM. Clin Chem 2005; Kahn et al., Diabetes Care 2005

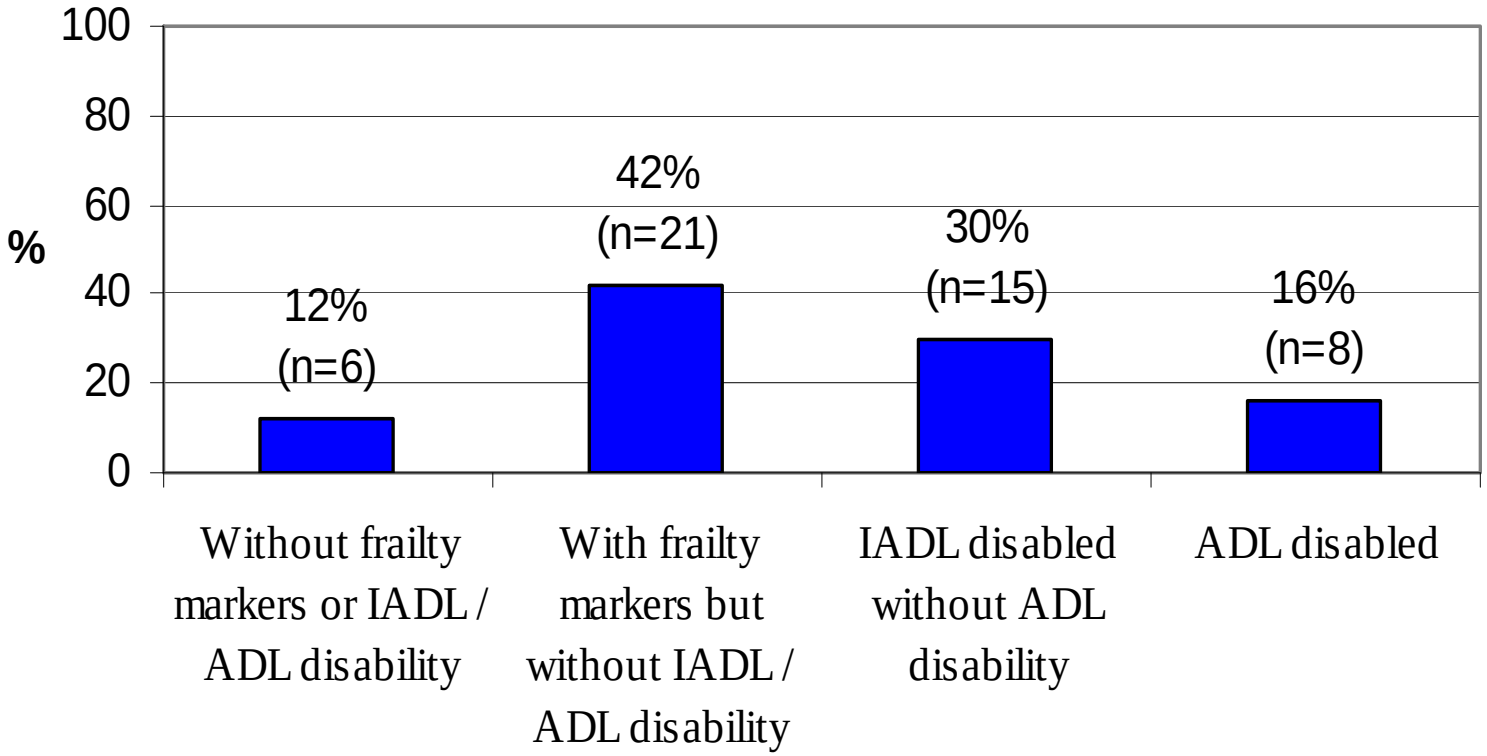
The Down Side of a Frailty Syndrome Missing the Trees for the Forest

- Lack of attention when only one component is present and definition of syndrome not met
- Persons with diseases/conditions that mimic frailty may be erroneously considered as frail
- Simple measure for vulnerability may be adequate
  - Gait velocity, grip strength
- Inappropriate use of diagnosis of frailty can
  - Alter self-concept; change others' perceptions; affect decision making inappropriately
- Non specific impact of aging, chronic disease and other risk factors

Relevance of the Frailty Syndrome

- Improves our understanding of the aging process and ability to characterise the heterogeneity of older persons
- At population and clinical level: characterises health and functional status beyond disability and co morbidity
- Identifies a subset of vulnerable older adults at high risk of *adverse outcomes*
  - Why some, at a given age, are vulnerable; others not
  - Varying degree of vulnerability with same chronic disease or disability
  - older persons who are functionally independent with apparently normal cognitive function may be overlooked even if they have identifiable frailty markers and are highly vulnerable for adverse health outcomes and increased utilisation of health services

Health and functional status of cancer patients, aged 70 years and older referred for chemotherapy- preliminary findings



Retornaz F, Monette J, Monette M, Sourial N, Wan-Chow-Wah D, Puts M, Small D, Caplan S, Batist G, Bergman H. Usefulness of frailty markers in the assessment of the health and functional status in older cancer patient referred for chemotherapy Journal of Gerontology:medical sciences. In Press

Relevance of the Frailty Syndrome

- Potential for modification, at least in early stages
  - Frailty and disability are dynamic states
  - opportunities for health promotion, prevention

Gill TM et al: N Engl J Med 2002

- Targeting risk in non disabled older persons with chronic disease
  - Understand health/functional characteristics
  - "Predict"/expect/plan outcomes and complications
  - Tailor intervention

Cacciatore et al. Eur J Clin Invest 2005

Ferrucci et al. Reviews in Oncology/Hematology 2003

Retornaz et al: JGeron med sci In Press

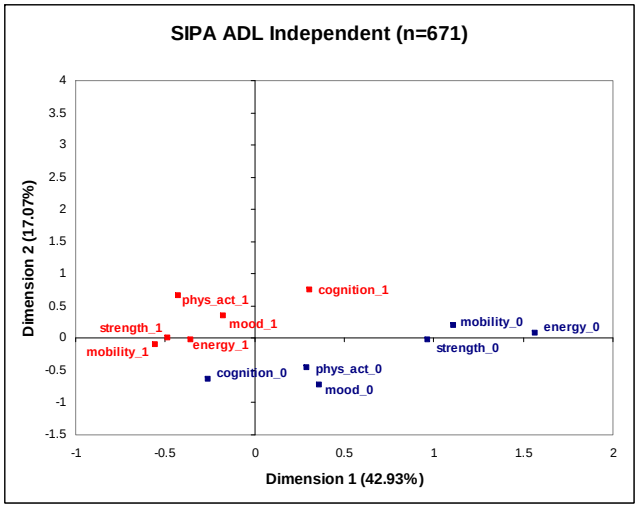
Further Research

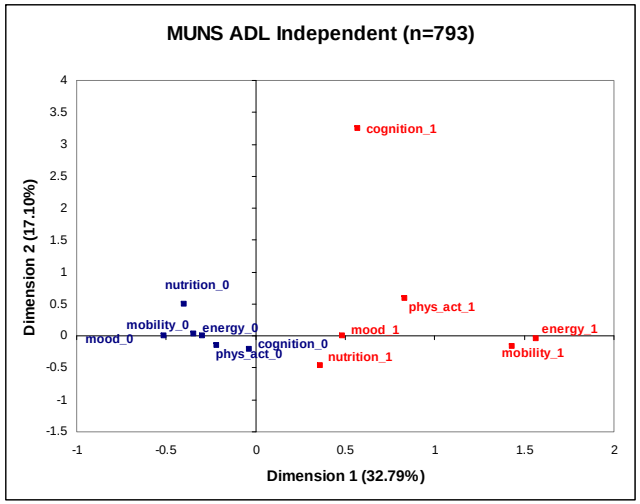
- Key questions
  - Do/how the candidate components cluster?
  - is the risk for adverse outcomes of the clustered components greater than the risk from the individual components?
  - underlying biological pathway?
  - role of psychosocial factors? interventions?
- Approach
  - Interdisciplinary collaborative networks; : biology, clinical, population health, social sciences, health services research

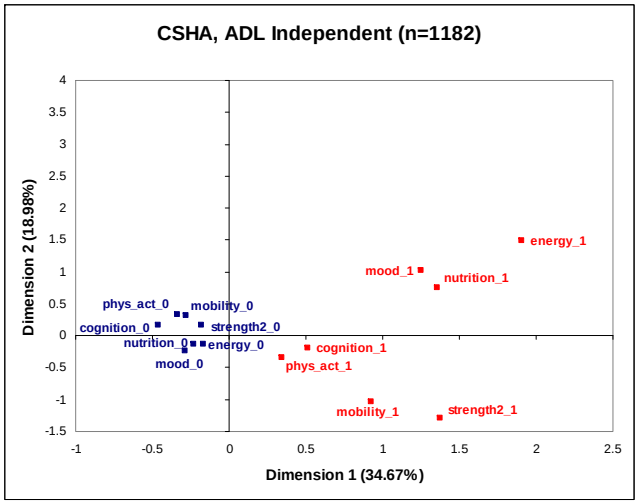
Further Research
Projects and Methodologies

- Design of novel longitudinal studies with a priori hypotheses
  - Frele, CLSA
  - Lausanne cohort
  - Kuh et al: Life course approach to healthy aging nine UK life course cohort studies.
- Systematic review-Canadian Initiative on Frailty and Aging
- Secondary analyses: FrData study: comparable approach to 10 international data base
- Clinical research: natural "experiments: impact of surgery, chemotherapy
- Biology; Animal models
- Clinical trials

FrData: Results excluding those with ADL disability







Wolfson C, Sourial N, Bergman H et al
Exploring the association among frailty domains in older persons. In Prepration

Conclusion

- Frailty research and debate has opened new horizons in understanding of the aging process, the heterogeneity of older persons and the potential to identify vulnerable older adults and prevent/delay adverse consequences
- Too early to close the debate
  - Frailty vs aging; which model
  - Frailty markers as markers of vulnerabilty
- Ultimately will only be relevant to clinicians, older individuals, and society if it succeeds in identifying effective health promotion, prevention, treatment, rehabilitation, and care interventions.

“I had come to an entirely erroneous conclusion, which shows my dear Watson, how dangerous it always is to reason from insufficient data.”

Sherlock Holmes in “The speckled band”

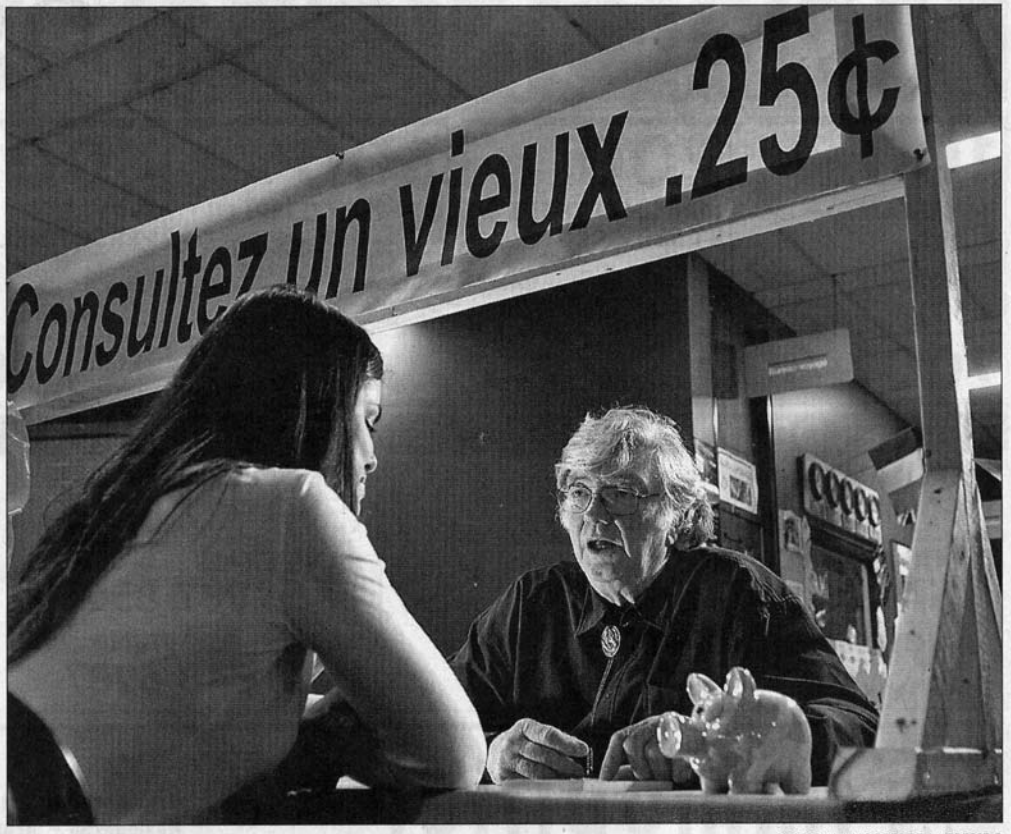


PHOTO ALAIN ROBERGE, LA PRESSE ©

Réjean Vanasse, un « vieux monsieur », vend sa sagesse 25 cents aux élèves du cégep Maisonneuve.

Parler à un vieux pour 25 cents

Funding/Support

- Max Bell Foundation
- CIHR
  - International development grant
  - Institute of Aging
- Réseau Québécois de recherche sur le vieillissement (Quebec Research Network on Aging) FRSQ
- Dr. Joseph Kaufmann Chair in Geriatric Medicine, McGill University
- Solidage (McGill/UdeM)-CIHR funded research team on frailty and aging
- Gustav Levinschi Foundation
- A large number of research groups and centers in Canada, Switzerland, Israel
- Canadian Geriatrics Society