

XIV Curso Academia Latino Americana de Medicina del Adulto Mayor

Epidemiology of Frailty

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Frailty in Older Adults

- **Dominant theme in Geriatrics**
 - Assessment, prevention, and management of frailty in older adults
- **Compression of morbidity in aging societies**
 - Efforts above and beyond traditional diseases
 - Disability
 - Falls
 - Short Physical Performance Battery
 - Sarcopenia

Frailty in Older Adults

- **Enhanced vulnerability**
 - Adverse Outcomes
 - Disability
 - Healthcare utilization
 - ER visits, recurrent hospitalization, LoS, NH admission
 - Mortality
 - Health status heterogeneity not explained by chronologic age or diseases
- **Distinct from “normal aging”**
 - “normal” vs. accelerated age-related functional decline

Operational Definition of Frailty

- **Evolving, varying approaches**
 - Conceptualization
 - Operational definition
 - Components of frailty models
 - Measurement of individual components
 - Purpose
 - Risk prediction, stratification
 - Outcomes being predicted
 - Setting
 - Study biologic underpinnings

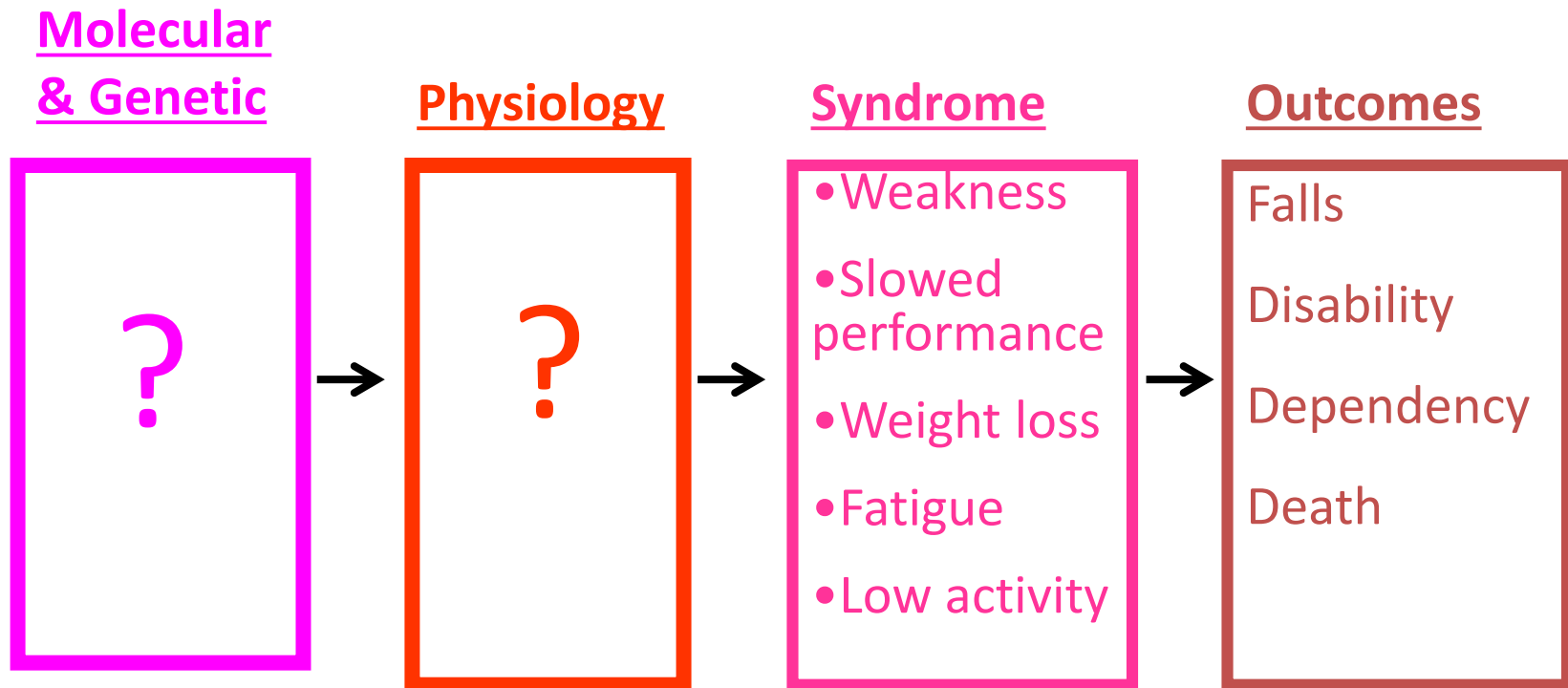
Frailty Phenotype

- **Distinct medical syndrome**
- **Increased clinical vulnerability**
 - Array of adverse health outcomes, including disability
- **Pathophysiologic basis**
 - Multisystem physiologic dysregulation
 - Reduced physiologic reserve compromising adaptation to stressors
- **Clinically recognizable**

CHS Frailty Phenotype Criteria: ≥ 3 of 5 items

- **“Shrinking”** - involuntary weight loss $>10\%$
- **Weakness** – grip strength $<20^{\text{th}}$ pctile
- **Slowness** – walking speed $<20^{\text{th}}$ pctile
- **Exhaustion** – CES-Depression Scale mod.
- **Decreased physical activity** – Minnesota Leisure Time Activity questionnaire –
– bottom 20^{th} pctile of calculated Kcal

Frailty Phenotype as a research tool



Fried and Walston, Principles of Geriatric Medicine and Gerontology (Wm Hazzard, Ed.) 1998.

Frailty Index

- **Accumulation of age-related health deficits that robustly predicts mortality, institutionalization**
 - Health deficit can be any symptom, sign, laboratory measurement, disease, or disability
 - E.g., comorbidities, psychosocial factors, disability indicators
- **Independent of the exact number, nature of deficits**
 - Flexibility regarding # of deficits available (20-50 deficits)
- **Continuous measure**
 - Derived from comprehensive geriatric assessment

Epidemiology of Frailty: Selected Aspects

- **Transitions in frailty status**
 - Frequent
 - More commonly from states of greater frailty than to states of lesser frailty
 - More commonly between adjacent states
- **Gradual, progressive deterioration – window of opportunity?**

Lee et al. JAMDA 2014.

Xue Q-L. Clin Geriatr Med 2011

Gill TM et al. Arch Intern Med 2006

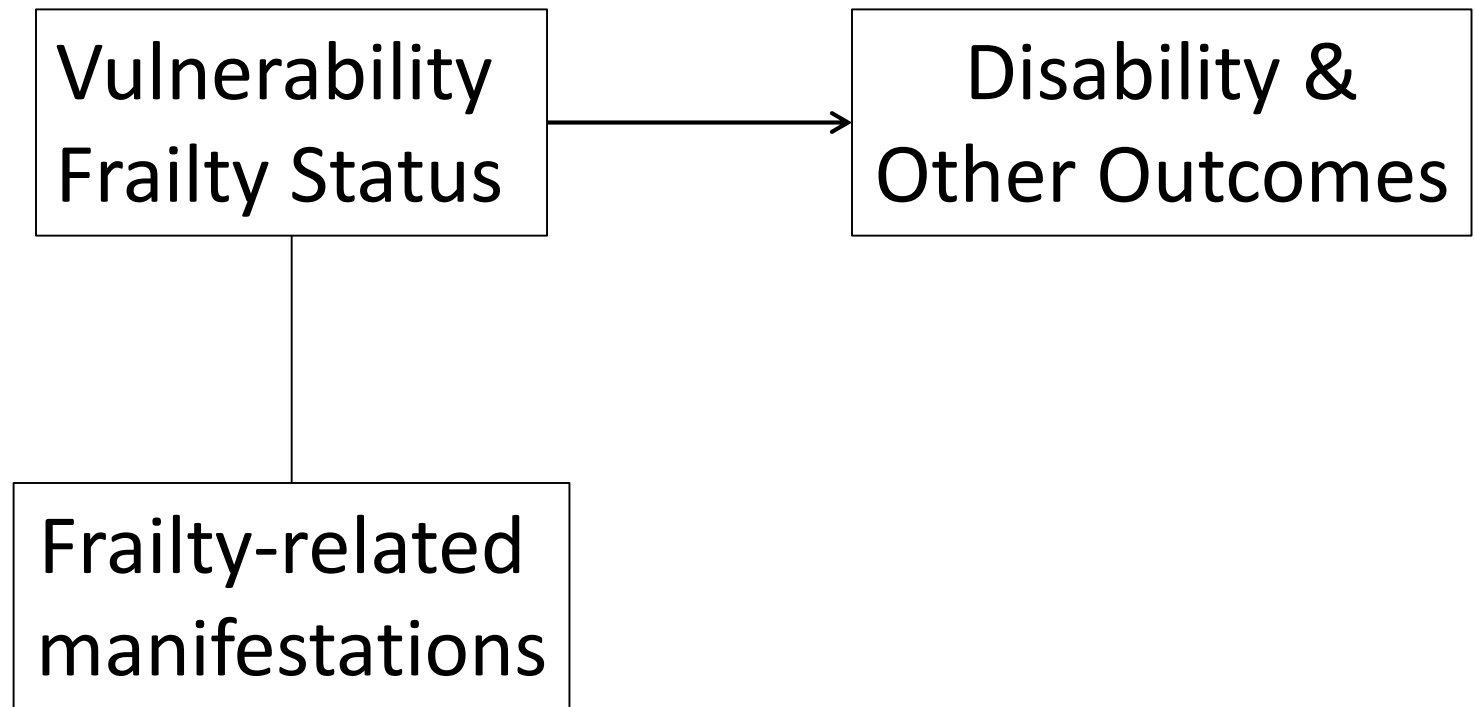
Espinoza et al. J Am Geriatr Soc 2012

Fallah et al. J Am Geriatr Soc 2011

Epidemiology of Frailty: Selected Aspects

- **Hierarchical order in the onset of frailty manifestations over time**
 - Weakness as the most common first manifestation
 - Occurrence of weakness, slowness, and low physical activity preceded exhaustion and weight loss

Is Frailty More than a Phenotype/Aggregate of Measures Indicating Vulnerability?



Is Frailty More than a Phenotype/Aggregate of Measures Indicating Vulnerability?

“NO”

- **Risk prediction as only goal**
 - e.g., risk stratification in healthcare systems for planning
- **Variables selection for vulnerability estimation**
 - All feasible that optimize risk prediction
 - Do not need to be thought of as “causal”,
 - Do not need to be biologically correlated
 - No need to attempt to distinguish between “frailty”, disability, falls, multimorbidity, falls, etc.
 - Still depends on outcome of interest
 - Disability, costs

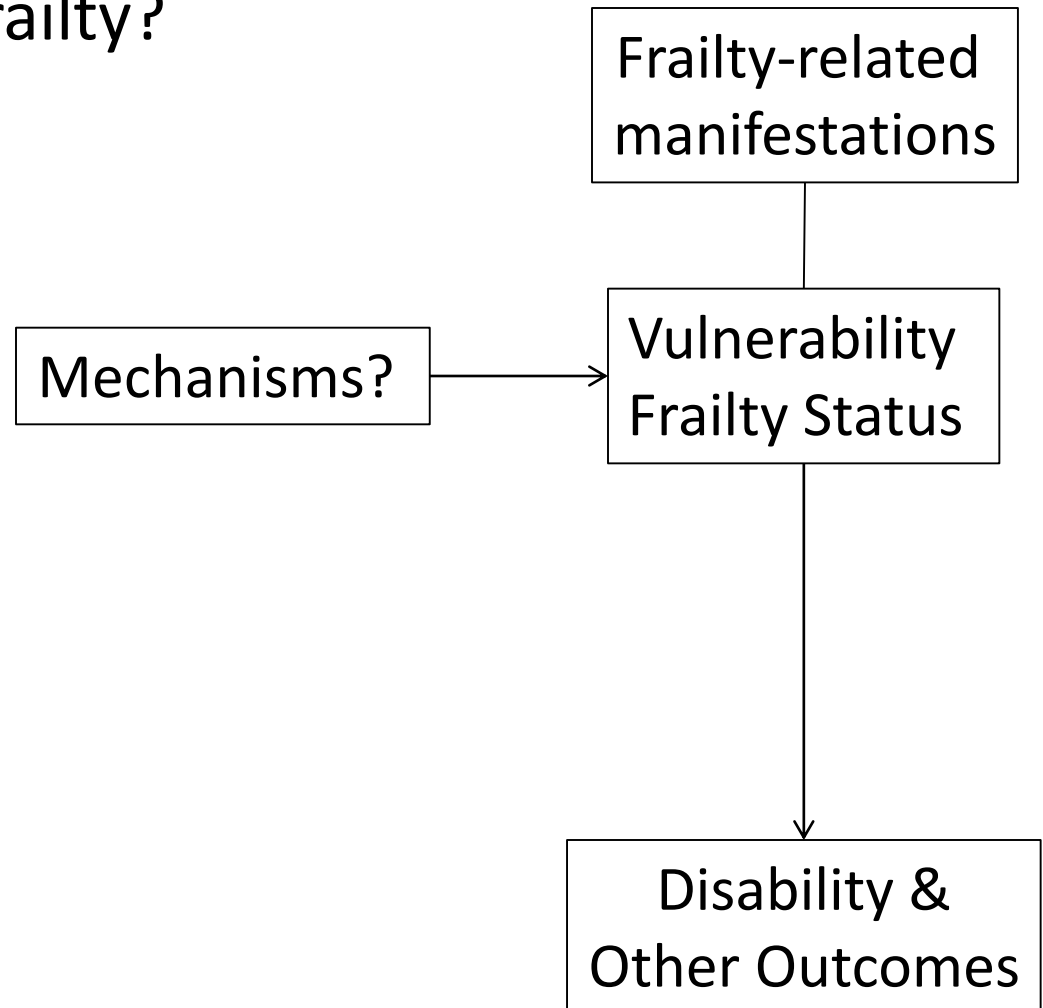
Is Frailty More than a Phenotype/Aggregate of Measures Indicating Vulnerability?

“YES”

- **Etiology and Treatment also as main goal(s)**
 - Risk stratification still a goal
- **Unique syndrome**
 - Distinct from disability or any other
 - Offers rationale for research seeking to identify pathophysiologic basis, and specific frailty interventions
- **Variables selection**
 - Among those hypothesized to be in a causal pathway
 - Correlation among variables given underlying mechanism

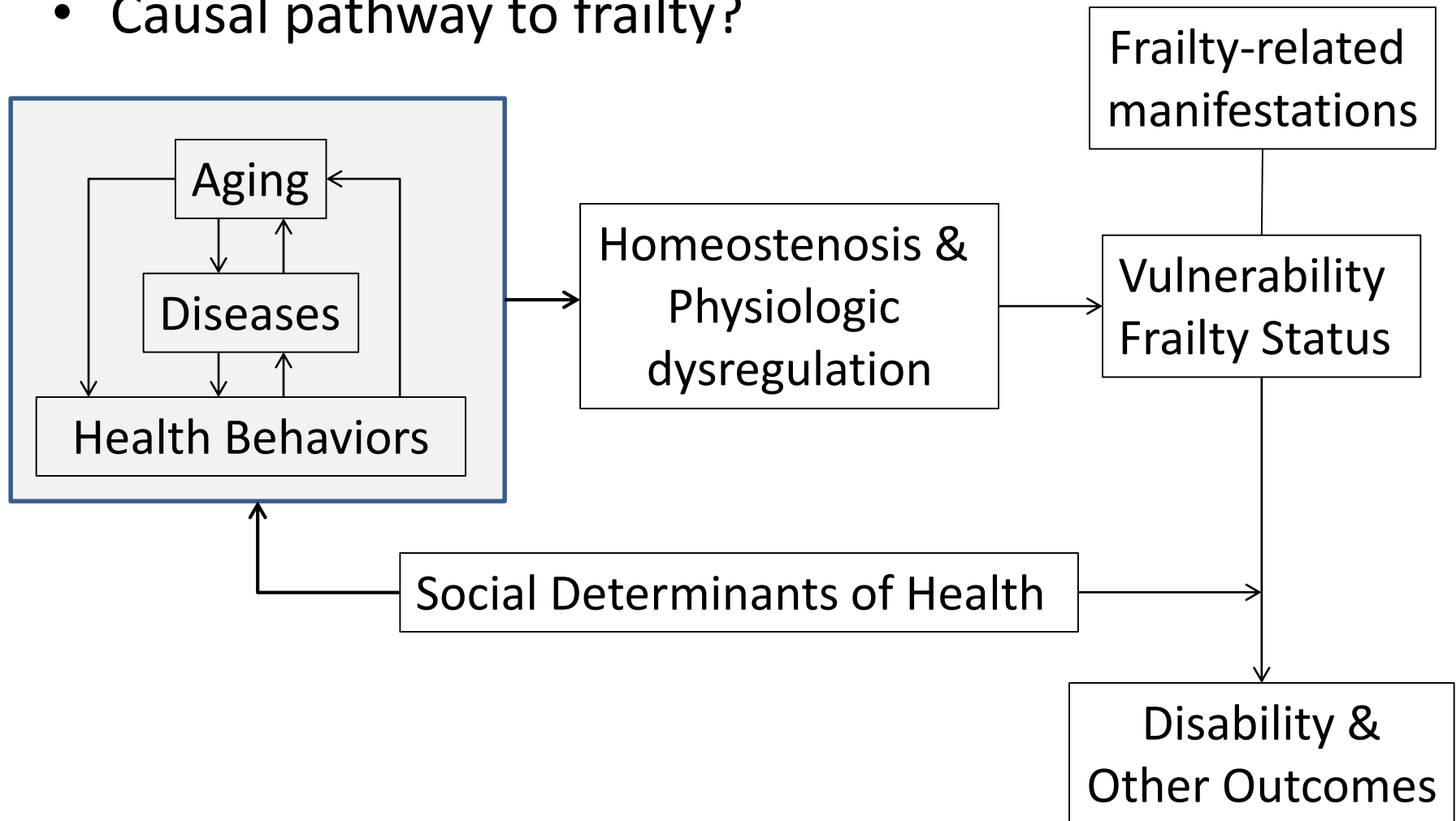
Frailty as A Unique Geriatric Syndrome

- Causal pathway to frailty?



Frailty as A Unique Geriatric Syndrome

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Age-Related Chronic Diseases and Frailty

- **Examples of age-related chronic diseases or conditions**
 - Cardiovascular disease
 - Diabetes
 - Osteoarthritis
 - COPD
 - “Obesity”
 - CKD (eGFR)

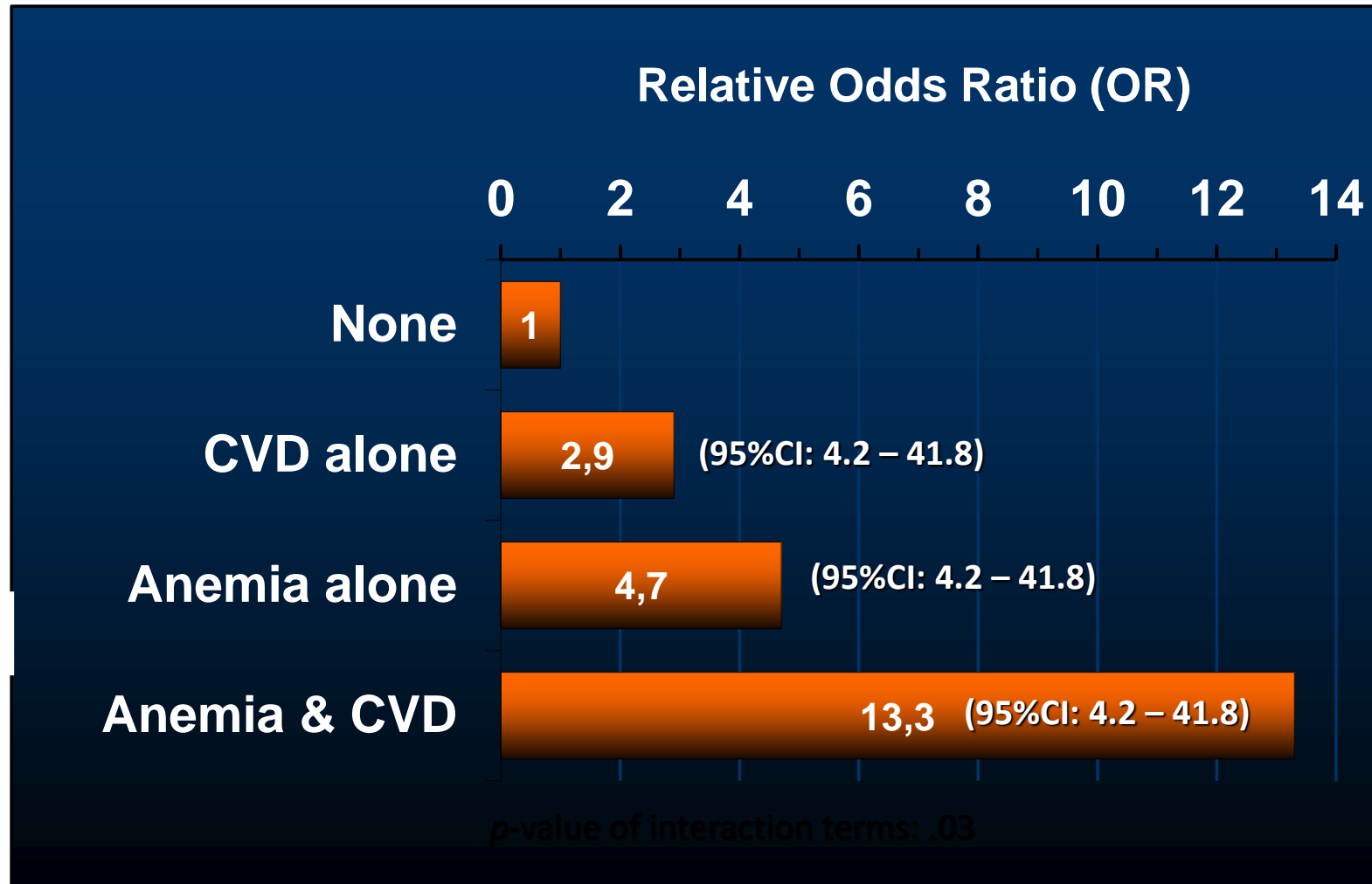
Subclinical Disease and Frailty

Age-, race-, and gender-adjusted ORs in elderly without CVD

Measure	OR	95% CI
Subclinical stroke per MRI	1.71	(1.15, 2.55)
Any major ECG abnormality	1.58	(1.10, 2.26)
LV motion abnormality on echo	2.47	(1.13, 5.39)
AAI		
<0.8 vs. >1.0	3.56	(2.03, 6.24)
≥ 0.8 and ≤ 0.9 vs. >1.0	2.01	(1.07, 3.76)
Carotid USG		
MIT-CCA (.5mm increase)	1.46	(1.00, 2.14)
MIT-ICA (.25 mm increase)	1.09	(1.02, 1.18)

Newman et al. J Gerontol A Biol Sci Med Sci. 2001 Mar;56(3):M158-66.

Conjoint Associations of Diseases



Adjusted for age, education, depression, MMSE, prevalent RA, and calculated GFR.

Adapted from Chaves et al. *J Gerontol A Biol Sci Med Sci*. 2005;60:729-735

Health Habits and Frailty

- Selected examples
 - Low physical activity
 - Diet
 - Deficient caloric and protein intake
 - Quality of diet
 - Mediterranean diet
 - Fruits and salad intake
 - Excessive alcohol intake

Social Determinants of Health and Frailty

- **Individual**

- Female gender
- Minorities
- Lower education
- Financial strain
- Loneliness
- Lower levels of social support
- Life space restriction
- Restricted access to care
- Reduced engagement in productive activities

Social Determinants of Health and Frailty

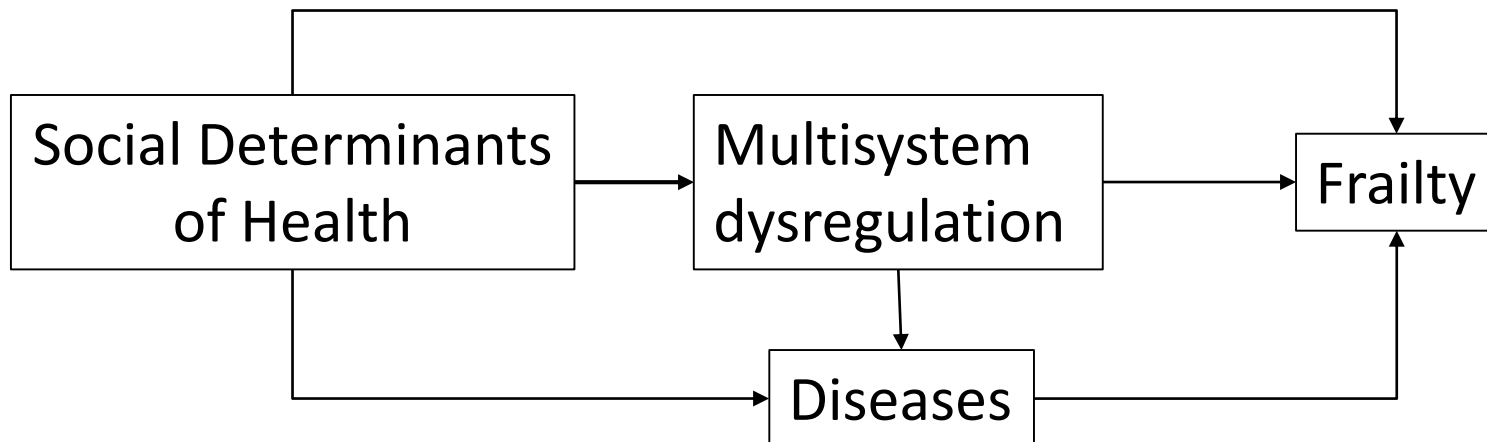
- **Neighborhood**

- Less ethnically dense neighborhood
- Deprived SES neighborhood

Aranda et al 2011

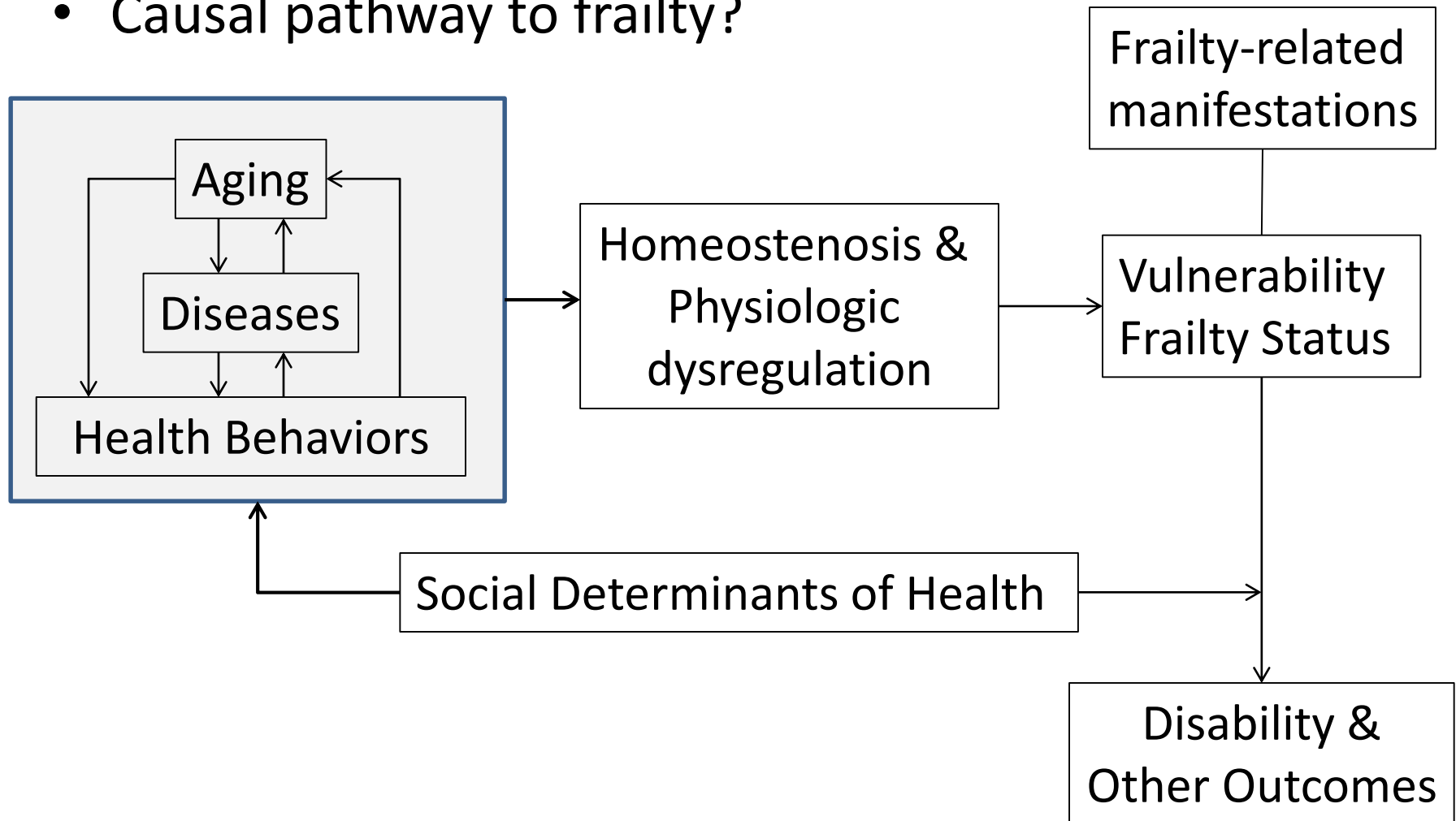
Lang et al. 2009

- **General Concept**

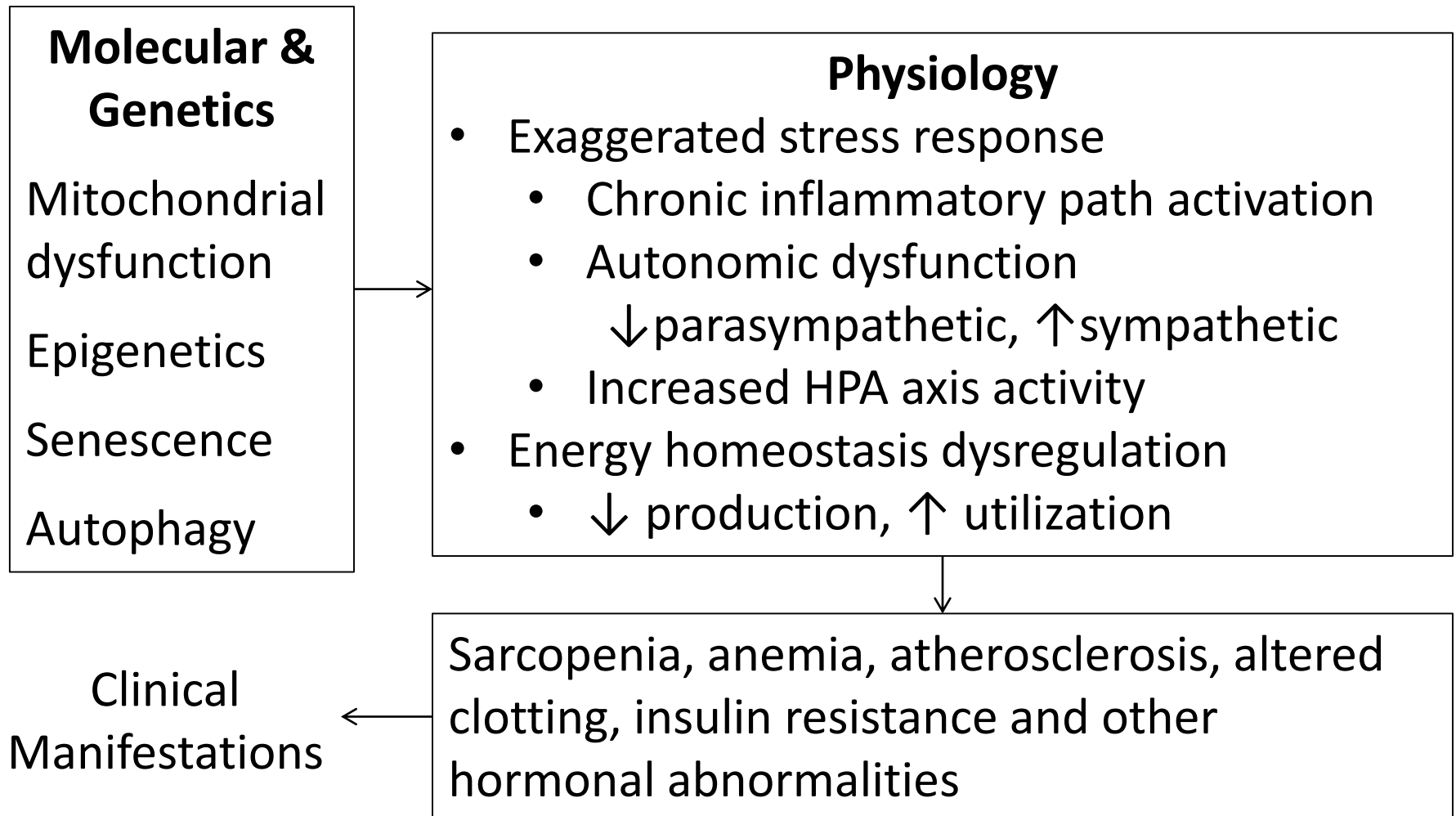


Frailty as A Unique Geriatric Syndrome

- Causal pathway to frailty?

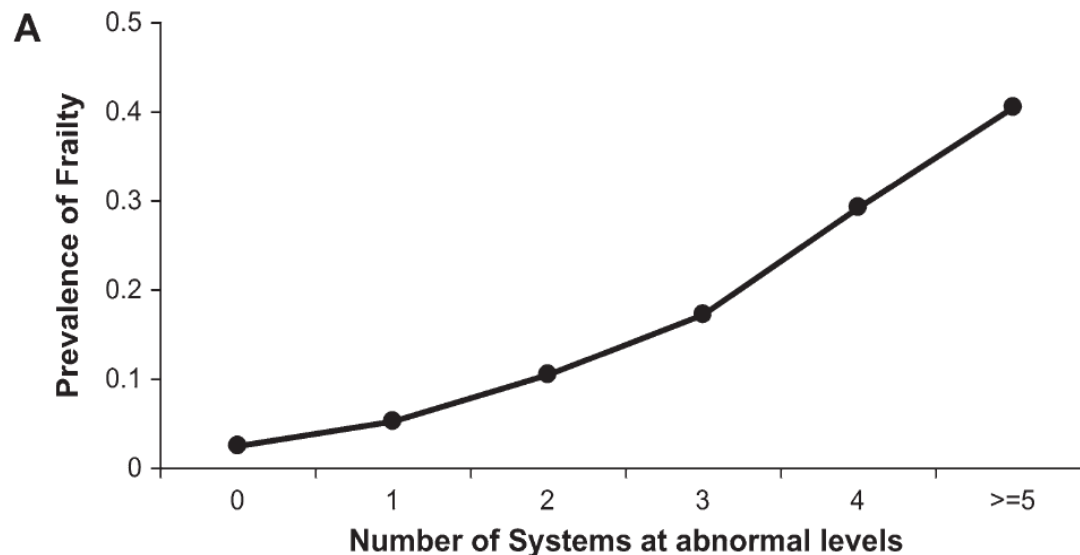


Mechanisms for Frailty: Molecular & Genetics & Physiology



Nonlinear Physiological Dysregulation and Frailty

- Independently, a number of systems shown to be associated with frailty
- Concurrently, aggregate impact on frailty status?



Adjusting for the level of each system measure, # systems impaired nonlinearly were associated with frailty

Cognition in the Definition of Frailty?

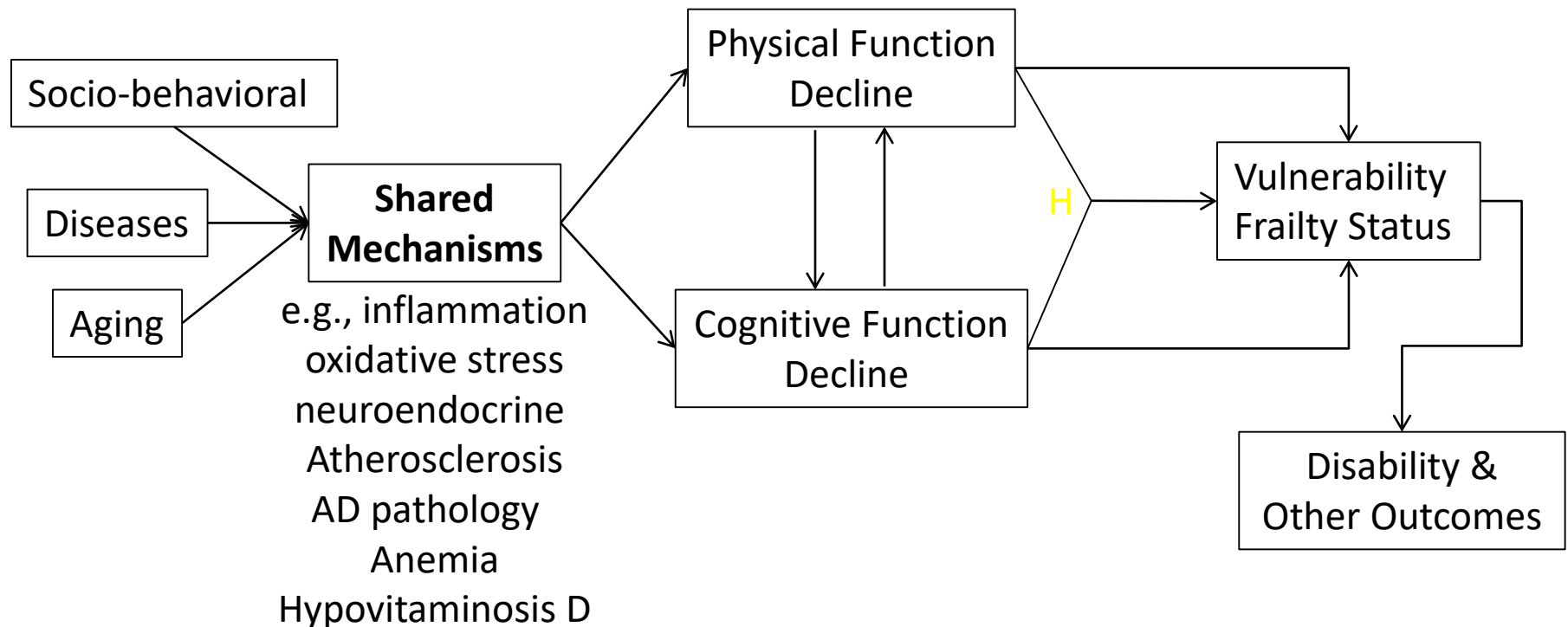
- **Prediction perspective**

- Cognitive impairment predicts adverse outcomes
 - Disability, Institutionalization, Hospitalization, Death
- Frailty and cognitive impairment are associated
 - Frailty predicts cognitive impairment
 - Cognitive impairment predicts frailty
- Addition of cognitive impairment indicator enhances prediction of adverse outcomes
- Is enhancement of predictive ability enough?

Cognition in the Definition of Frailty?

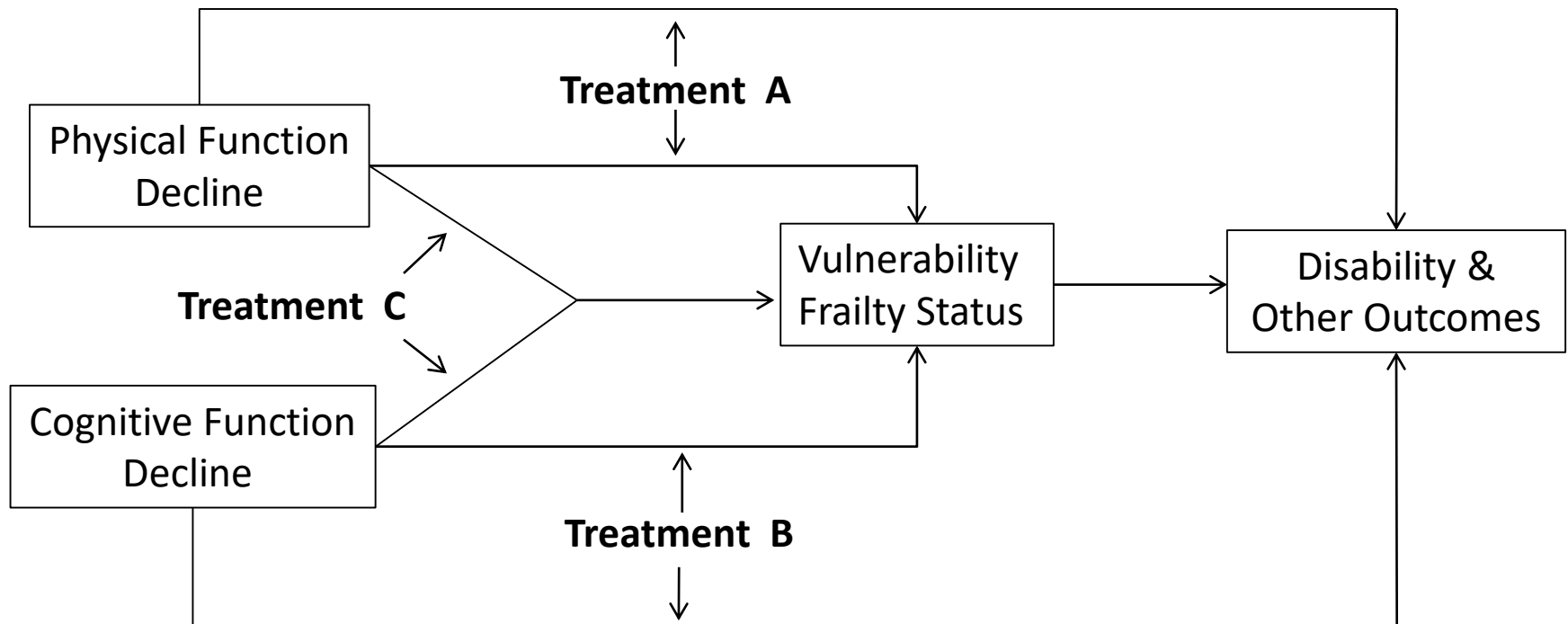
- **Biological perspective**

- Common underlying pathophysiology of which physical and cognitive decline are manifestations?



Cognition in the Definition of Frailty?

- **Treatment perspective**
 - Too distinct effect of treatment on physical function and cognitive function pathways?



Frailty in Older Adults

- **Frailty at the core of geriatric medicine**
- **Frail older adults at risk for adverse health outcomes**
 - Excess vulnerability not explained by presence of chronic diseases alone or chronological age
- **Opportunity for intervention**
 - Screening and intervention may lead to improved quality of life, lower costs

Frailty in Older Adults

- **Major advances**
 - Conceptual frameworks & operational definitions
 - Study of the epidemiology of frailty
 - Insight into the etiology of frailty and potentially modifiable risk factors
 - Use for risk stratification in clinical decision-making
 - Surgery, Diabetes, Hypertension
 - Geriatric Frailty Clinic
 - Target population for RCT

Frailty in Older Adults

- **Lack of consensus on one operational definition should not be a deterring factor**
 - Major problem for design of trials targeting frailty as primary outcome
 - Natural history of clinical investigation
 - Complementary, evolving approaches
 - Test of time: What works?
 - Improves quality of life
 - Reduce costs

Frailty in Older Adults

- Limited knowledge, clinical trial data
 - Frailty prevention and/or reversal, and disability prevention and/or postponement
- Mostly indirect
 - Frailty components (e.g., strength) as targets and frailty outcomes (e.g., mobility disability)
- Most robust evidence to reduce vulnerability
 - Exercise; i.e., strength and aerobic

Exercise Training and Nutritional Supplementation for Physical Frailty in Very Elderly People

Fiatarone et al. NEJM 1994

- Randomized, placebo-controlled trial
- 10 weeks, n=100
- Long Term care Facility residents without severe cognitive impairment
- Lower-extremity resistance training and/or multi-nutrient supplement (10 weeks
- Placebo (recreational) activity and placebo supplement

Exercise Training and Nutritional Supplementation for Physical Frailty in Very Elderly People

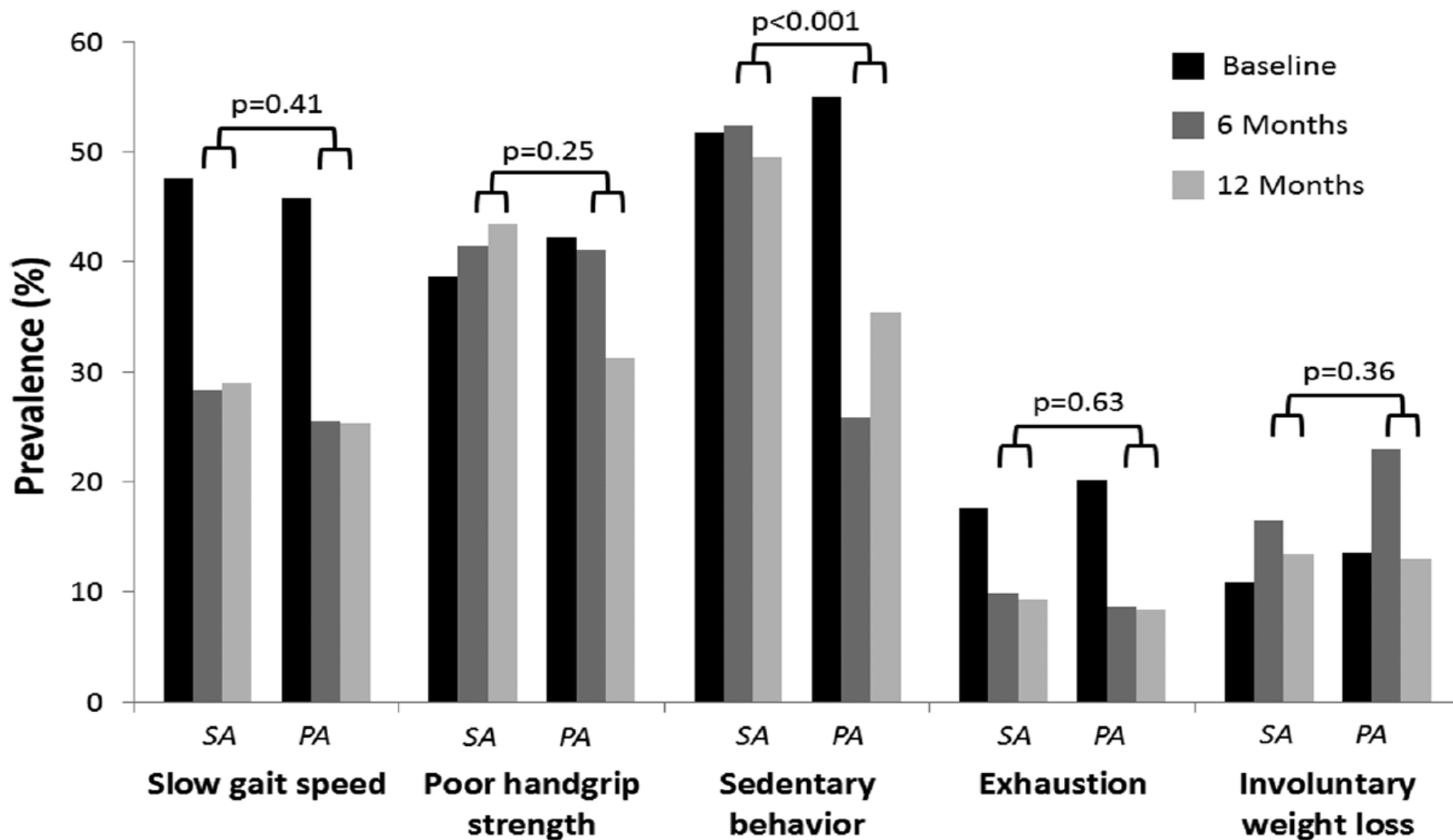
Fiatarone et al. NEJM 1994

- Selected Characteristics in Exercise Group
 - Mean age: 86.2 years old
 - Mean Length of stay: 9 months
 - Mean Gait speed: .51 m/sec
 - Falls in past year: 72%
 - Level of care received:
 - 32% independent
 - 64% semi-dependent
 - 4% dependent

LIFE-P Trial and Frailty

- RCT, physical activity vs. successful aging
 - 25 weeks
- Community-dwelling
- Aged 70-89 years
- Sedentary
 - < 20 min/week in regular physical activity
- SPPB \leq 9

LIFE-P Trial and Frailty



Epidemiology of Frailty Research Agenda

- **Need for clinical trial data to guide inclusion of specific components of multifactorial interventions**
 - Vitamin D
 - Testosterone and other hormones
 - Myostatin inhibitors
 - Nutrition
 - Anti-inflammatory agents
 - Angiotensin II receptor blockers (ARBs) that target RAS dysregulation

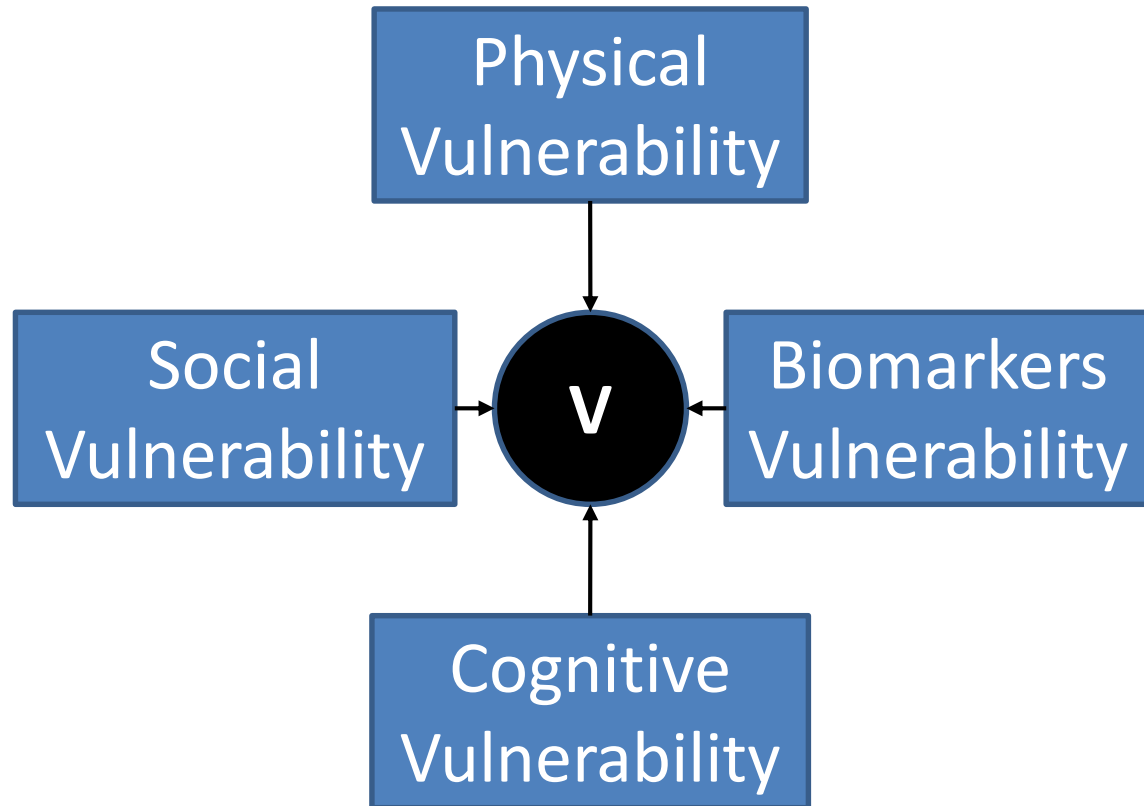
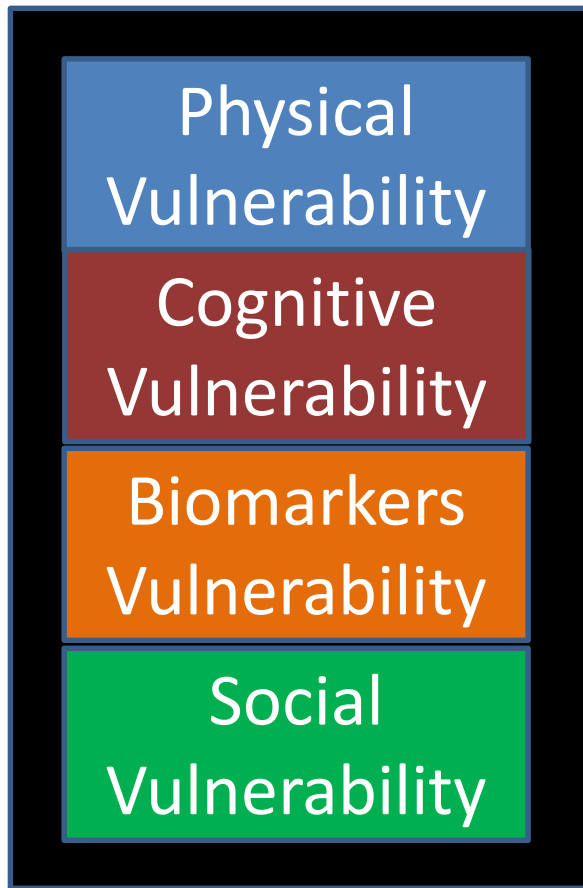
Epidemiology of Frailty Research Agenda

- **Need for improved understanding about physiologic and molecular changes that drive the pathogenesis of frailty**
 - Target pathways
 - Clinical assessment tools
 - Novel, early treatments
- **FRAILOMIC initiative**
 - Insight into factors that turn frailty into disability
 - Enhance clinical prediction

Epidemiology of Frailty Research Agenda

- **Enhance knowledge about social determinants of health across the life course**
 - From early childhood to late-life
- **Research integrating assessment-intervention of social determinants of health and medical factors**

Frailty Vulnerability: One or more?



Translational Epidemiology & Frailty

- **Need for data on the added value of frailty assessment for clinical decision-making**
 - Clinical tool for risk assessment before surgery
 - Consequences of raising awareness?
- **Geriatric Frailty Clinic at the Gerontopole de Toulouse as a major moving forward initiative**
 - Medical condition that needed a new intervention in more than 50% of the patients
 - Therapeutic changes, Recommendations
 - Nutrition, physical activity, social, specialist

Translational Epidemiology & Frailty

- **Geriatric Frailty Clinic at the Gerontopole de Toulouse as a major moving forward initiative**
 - Preliminary insight on Outcomes, Costs
 - Experience from redesigning healthcare delivery
 - Coordination of multifactorial assessment & intervention
 - Refinement of tools to identify those who may benefit the most
 - Intervention components
 - RCT testing added value of frailty

Translational Epidemiology & Frailty

- **Reshaping healthcare delivery system**
 - Integrated, coordinated care
 - Quality of life
 - Efficient, sustainable
 - Innovation
 - Culture
 - Policies & Reimbursement models
 - Bridges community-clinical setting – academia & other stakeholders
 - Expansion of prevention opportunities

Examples of Other Vulnerability Indices

- Vulnerable Elders Survey (VES-13) *
 - Simple screening tool to identify community-dwelling older persons at risk for health deterioration
 - Age, self-rated health, disability
- Index for measuring overuse of healthcare resources with Medicare claims data **

* Saliba et al. JAGS 2001

** Segal et al. Med Care 2014

Frailty in Older Adults

- Frailty concept, prevention, and treatment at the core of geriatric medicine
- Excess vulnerability
 - Not explained by presence of chronic diseases alone or chronological age
 - Late-life health status heterogeneity
 - Does not distinguish between frailty, disability, and comorbidities

Frailty in Older Adults

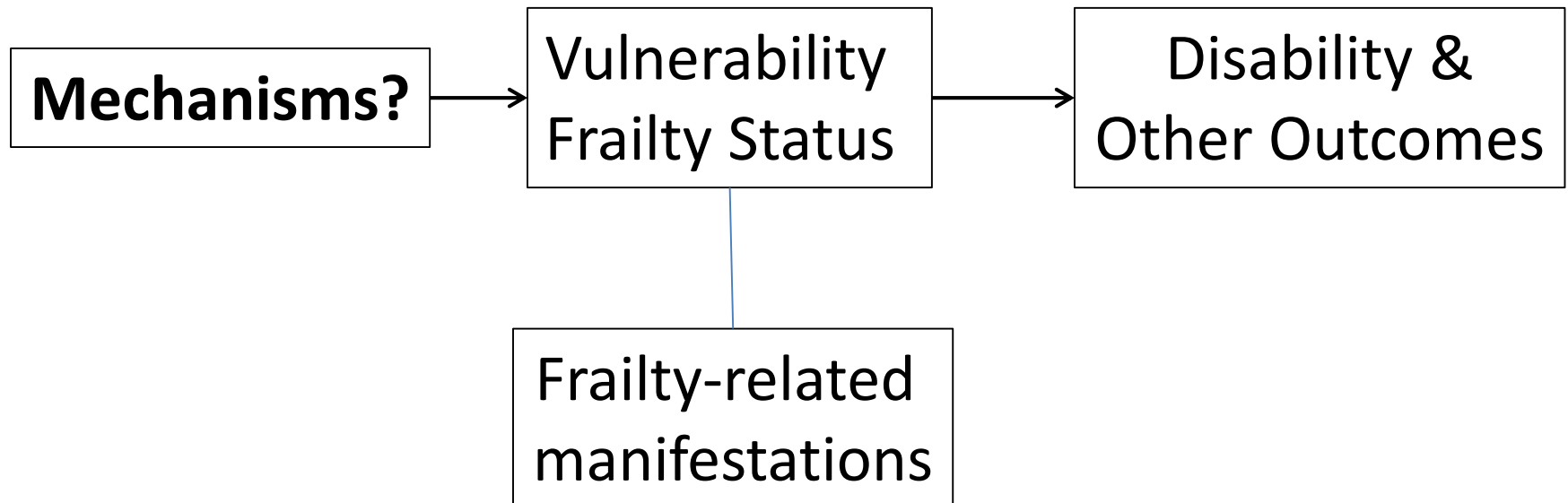
- Proposed as geriatric syndrome
 - Common
 - Causal contributor to disability, adverse outcomes
 - Underlying mechanism
 - May offer a novel intervention approach
 - Frailty prevention and/or reversal, disability prevention
 - Quality of life
 - Healthcare utilization

Mechanisms for Frailty: Molecular & Genetics & Physiology

- Aggregate effects and complex interactions across systems essential to homeostasis
- Different levels Physiologic dysregulation
 - Molecular/genetic
 - Physiologic
 - Clinical presentation and vulnerability

Frailty as A Unique Geriatric Syndrome

- Causal pathway to frailty?



EPIDEMIOLOGY OF FRAILTY

- Primary vs. secondary frailty
 - Severe impairment in single system; ie, “secondary frailty”
 - Mild-to-moderate impairments in multiple physiologic systems; ie, “primary frailty”

Considerations and Implications for Assessment of Frailty Status in older adults?

Main Goal: Risk Prediction

No

Is Frailty More than a Phenotype/Aggregate of Measures Indicating Vulnerability?

- Risk prediction is the Goal If the answer is “No”
- All possible (feasible) variables that maximize risk prediction, stratification
- Variables do not need to be thought of as “causal”
- Variables do not need to be biologically correlated among themselves
- Don’t even need to be Medical
- Do not need to attempt to distinguish between “frailty”, disability, falls, multimorbidity, falls, etc. in the context of healthcare services utilization
- Context Example: Risk stratification in healthcare

Where could we be in ten years?

- Frailty syndrome(s) in ICD-x?
- Frailty syndrome(s) as FDA-accepted indications for interventions?
- Highly effective treatments for frailty?
- Frailty prevention strategies?

It could happen.

Frailty Research Agenda

- What reduces vulnerability?
- Exercise
- Improved understanding about physiologic and molecular changes that drive the pathogenesis of frailty
 - Target pathways
 - Clinical assessment tools
 - Novel, early treatments above and beyond disease-specific approaches
- FRAILOMIC initiative
 - Large scale research project aiming to identify the <http://www.frailomic.org/>

Mechanisms for Frailty: Molecular & Genetics & Physiology

- Aggregate effects and complex interactions across systems essential to homeostasis
- Different levels Physiologic dysregulation
 - Molecular/genetic
 - Physiologic
 - Clinical presentation and vulnerability
- Mitochondrial dysfunction
- Autophagy
- Oxidative stress
- Inflammation
- Telomere dysfunction

Risk Factors for Frailty: Molecular & Genetics

- Mitochondrial dysfunction
- Autophagy
- Oxidative stress
- Inflammation
- Telomere dysfunction
- Immuno dysfunction
- Autonomic dysfunction
- Loss parasympathetic, increased sympathetic
- Neuroendocrine

Physiologic impairments in frailty Association of abnormal levels in multiple physiological systems with frailty

- Sarcopenia
- Inflammation
- Decreased heart rate variability
- Altered clotting processes
- Altered insulin resistance
- Anemia
- Altered neuroendocrine axis:
 - cortisol response to stress

Evidence to date: Biomediators associated with frailty syndrome

- Independent: IGF1, IL-6, anemia, clotting factors, insulin resistance, undernutrition
- Pairwise: IGF1 * IL-6
- Parallel: DHEAS, IGF1, IL-6

- Muscle
- Inflammation
- Hormones
- Vitamin D
- Anemia
- Comprehensive geriatric management

A number of systems independently
associated with frailty.

Does dysregulation of multiple systems
concurrently have an aggregate effect on
frailty?

Increasing number of systems at adverse levels associated with frailty phenotype

Hypothesized Pathway to Frailty and Loss of Independence in Older Adults

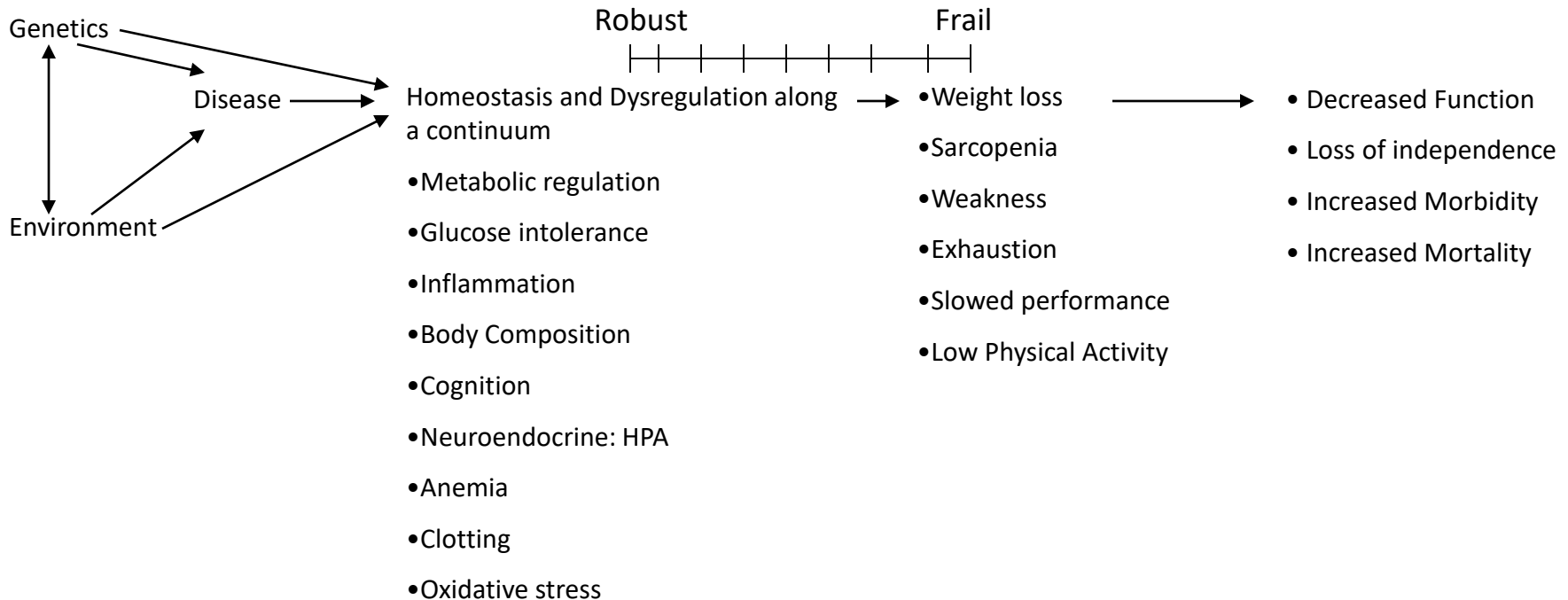
Ultimate Causes

Subclinical Components and Mechanisms

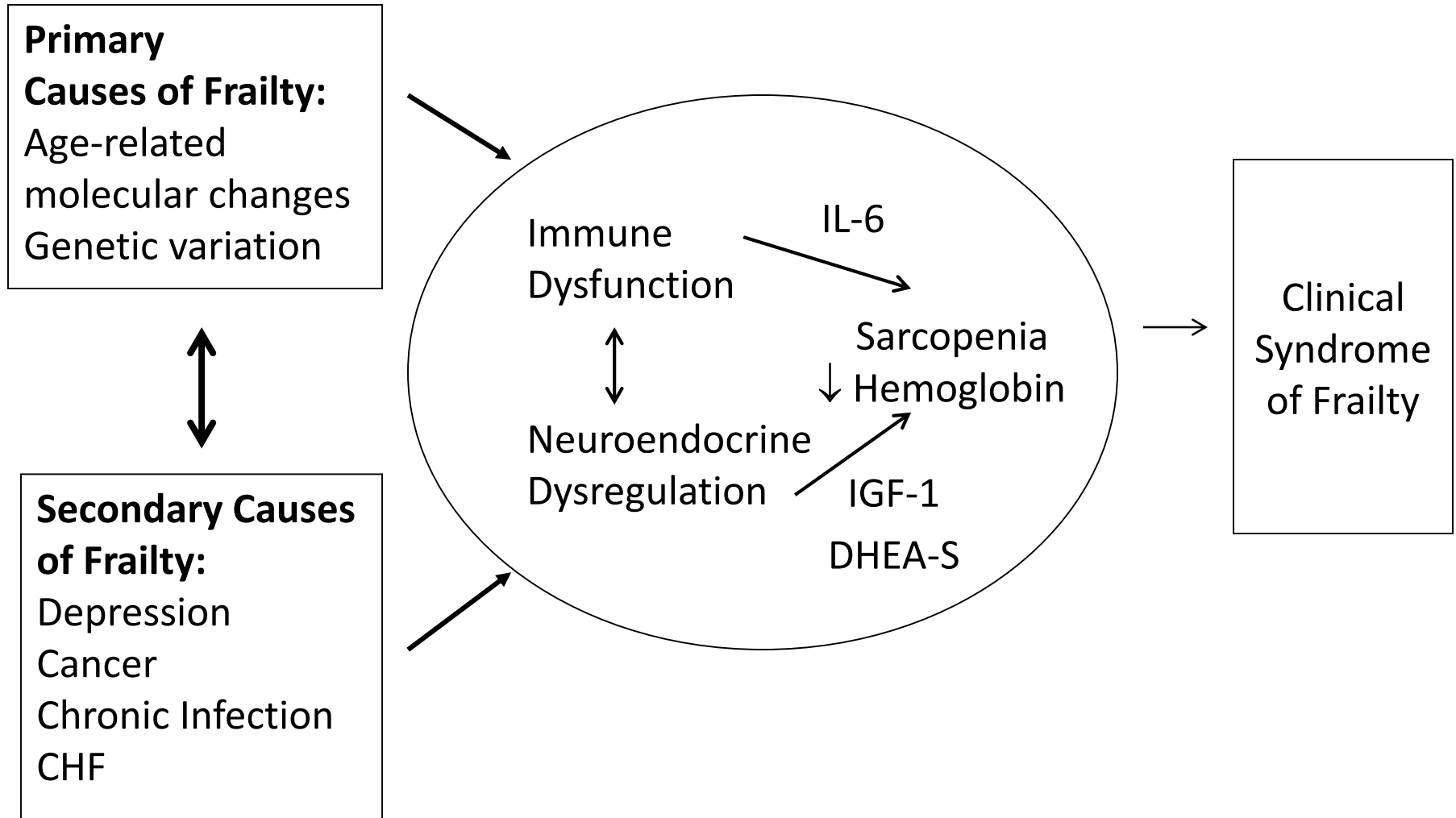
Clinically Observable Syndrome

Distal Outcomes

RESILIENCY



Causal Pathway 2003



FRAILTY

- Hallmark→ decreased physiologic reserve
 - Severe impairment in single system; ie, “secondary frailty”
 - Mild-to-moderate impairments in multiple physiologic systems; ie, “primary frailty”

FUTURE DIRECTIONS

- Mechanisms that constitute the pathophysiologic basis of frailty
- How physiologic systems interact and target signals
- Opportunity to prevent or reverse frailty?
- Strongest evidence for exercise
- Integrate frailty, disability, and sarcopenia
- Comprehensive geriatric assessment

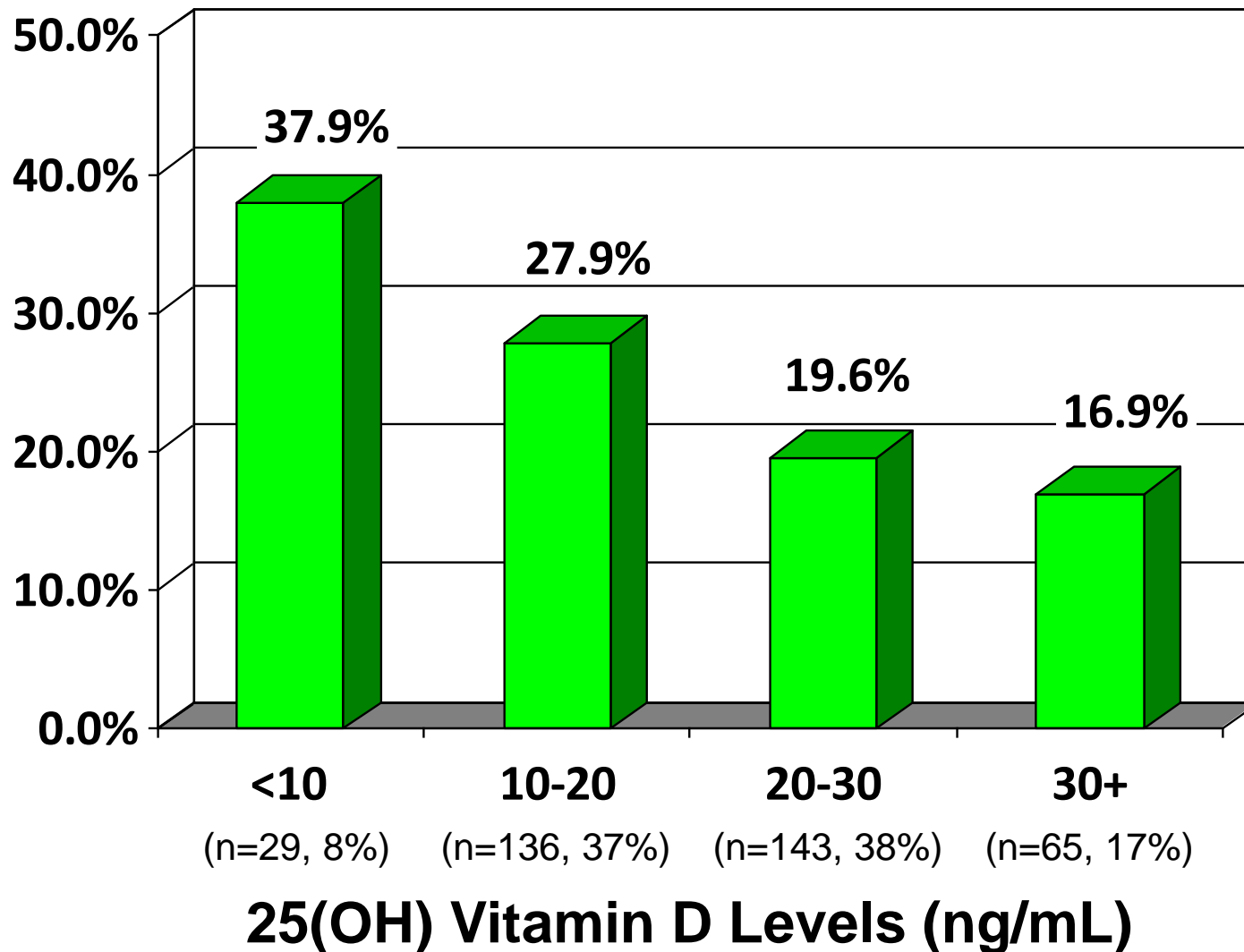
FRAILITY IN OLDER ADULTS

- Frailty concept, prevention, and treatment at the core of geriatric medicine
- Increasing recognition
 - Geriatrics & expanding into other specialties
- Common geriatric syndrome that may offer a novel opportunity for disability prevention in aging societies
 - Impact on quality of life
 - Healthcare utilization

FRAILITY IN OLDER ADULTS

- **Excess vulnerability**
 - Late-life health status heterogeneity
 - Does not distinguish between frailty, disability, and comorbidities
- **Proposed as geriatric syndrome**
 - Causal contributor to disability, adverse outcomes
 - Underlying mechanism
 - Target for intervention
 - Frailty prevention and/or reversal
 - Disability prevention

Cumulative Incidence of Incident Frailty Per Baseline Vitamin D Levels Median follow-up time ~ 9 years



Adjusted* Relative Hazards of Incident Frailty

25(OH)D Level, ng/mL	RR	95%CI	p-value
<10	1.0	—	—
10-20	.67	.34-1.3	.261
20-30	.42	.20-.88	.022
30+	.39	.16-.95	.039

* Adjusted for age, race, education, CVD, diabetes, depression (GDS), hip/knee OA, and MMSE scores

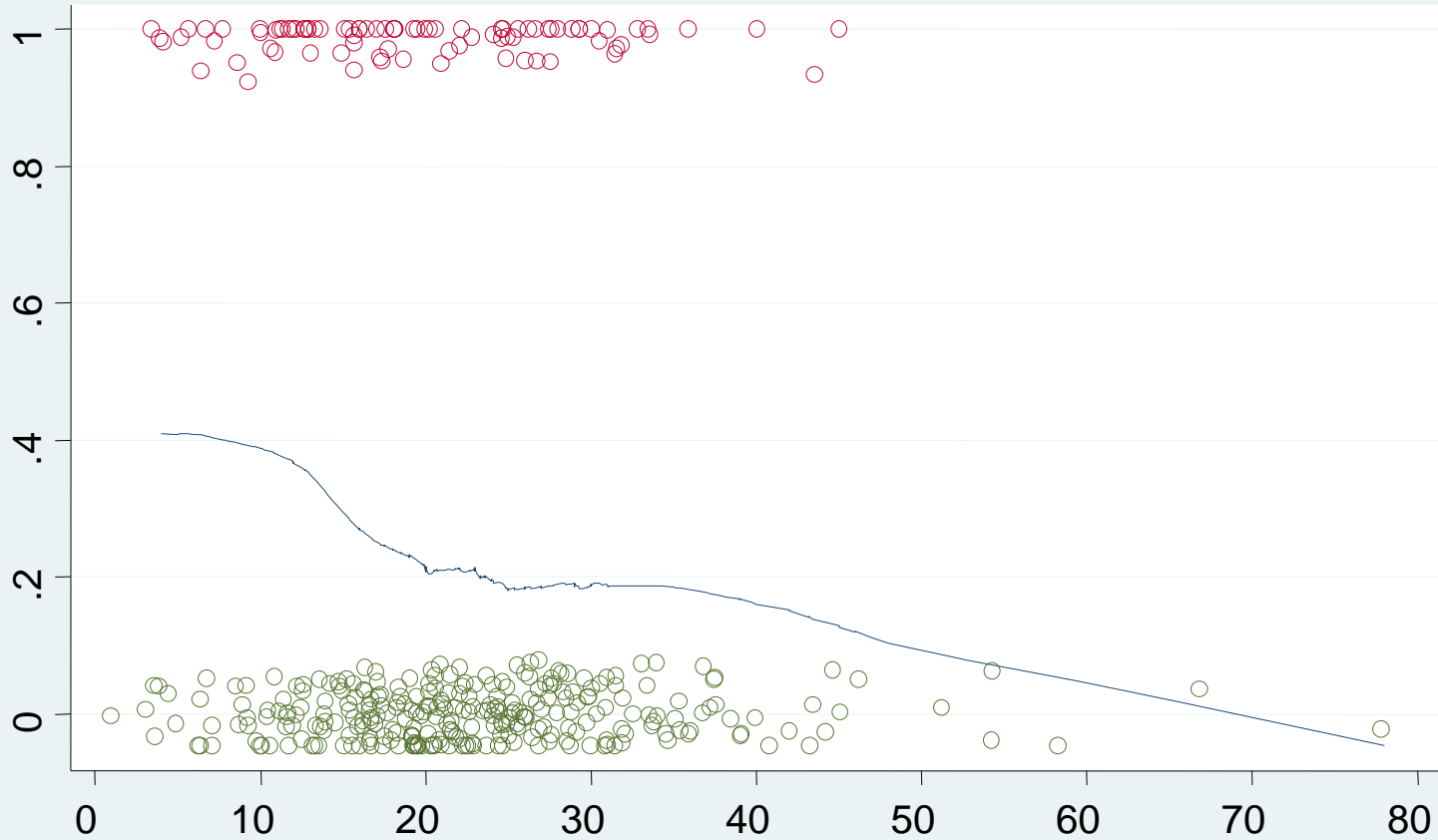
Adjusted* Relative Hazards of Incident Frailty

Serum 25(OH)D, ng/mL	RR	95%CI
15	1.0	Reference
20	.83	.73-.96
25	.69	.53-.91
30	.58	.39-.86
35	.48	.28-.82

* Adjusted for age, race, education, CVD, diabetes, depression (GDS), hip/knee OA, and MMSE scores

Cumulative risk of incident frailty across the continuous distribution of serum 25(OH)D

Probability of Frailty



Serum 25-hydroxyvitamin D (ng/mL)

Concept – Definition-Application

- Concept of Frailty: one or many?
- Vulnerability at-risk
- Syndrome
- Multifactorial
- Etc.

- Research on frailty received a tremendous push with the introduction of a standardized, valid operational definition for frailty
- Fried
- Rockwood

Translational Epidemiology

Slide from Linda on frailty investigation?

Distribution

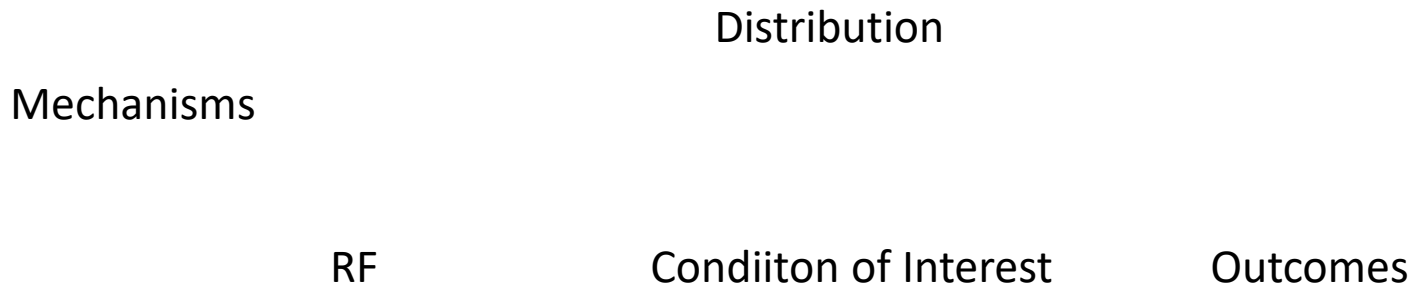
Mechanisms

RF

Condition of Interest

Outcomes

Traditional Epidemiology



Message: without knowing well what that is, it does not make sense –
focus on concept

Slide from Gordis?

Comprehensive
Geriatric
Assessment

Frailty

Falls
Disability
Frailty
Sarcopenia
Comorbidity

Different measures for different applications

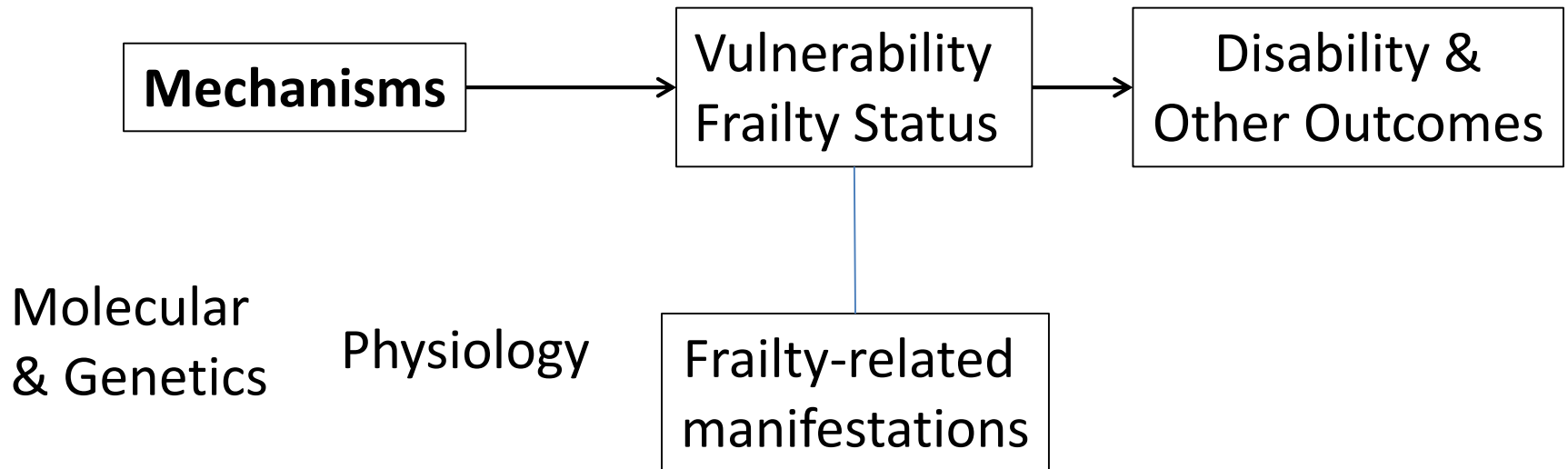
Opportunities for prevention

- Primary
- Secondary
- Tertiary

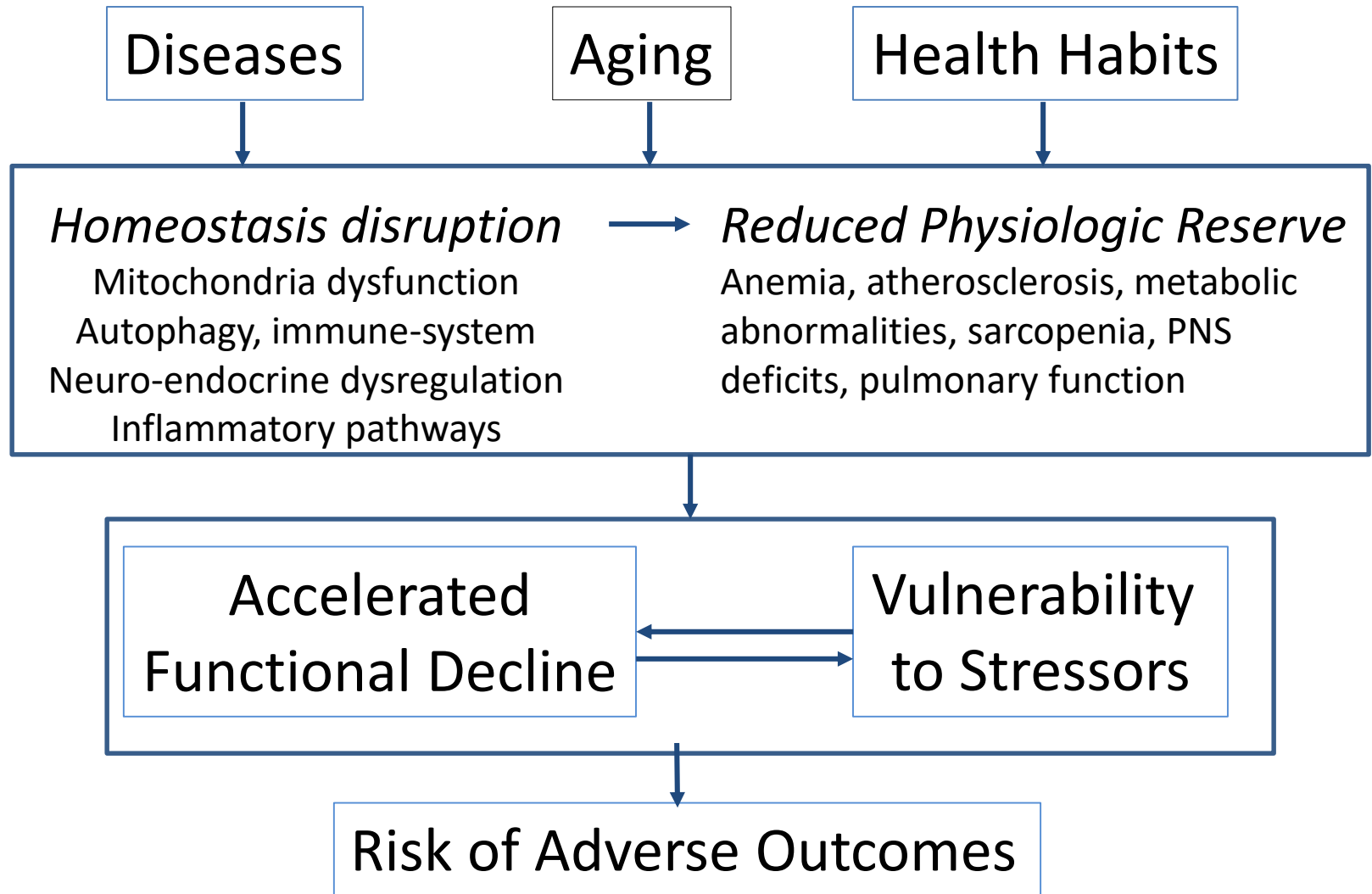
- Primary care setting
- Geriatricians, GP,
- Frailty clinics
- Above and beyond usual care

Frailty as a Unique Geriatric Syndrome

- Causal pathway to frailty?



Concept of Frailty



Falls, Disability, NH admission, Hospitalization, Mortality

Frailty as a Unique Geriatric Syndrome

- Causal pathway to frailty?

Mechanisms
Homeostenosis &
Physiologic
dysregulation

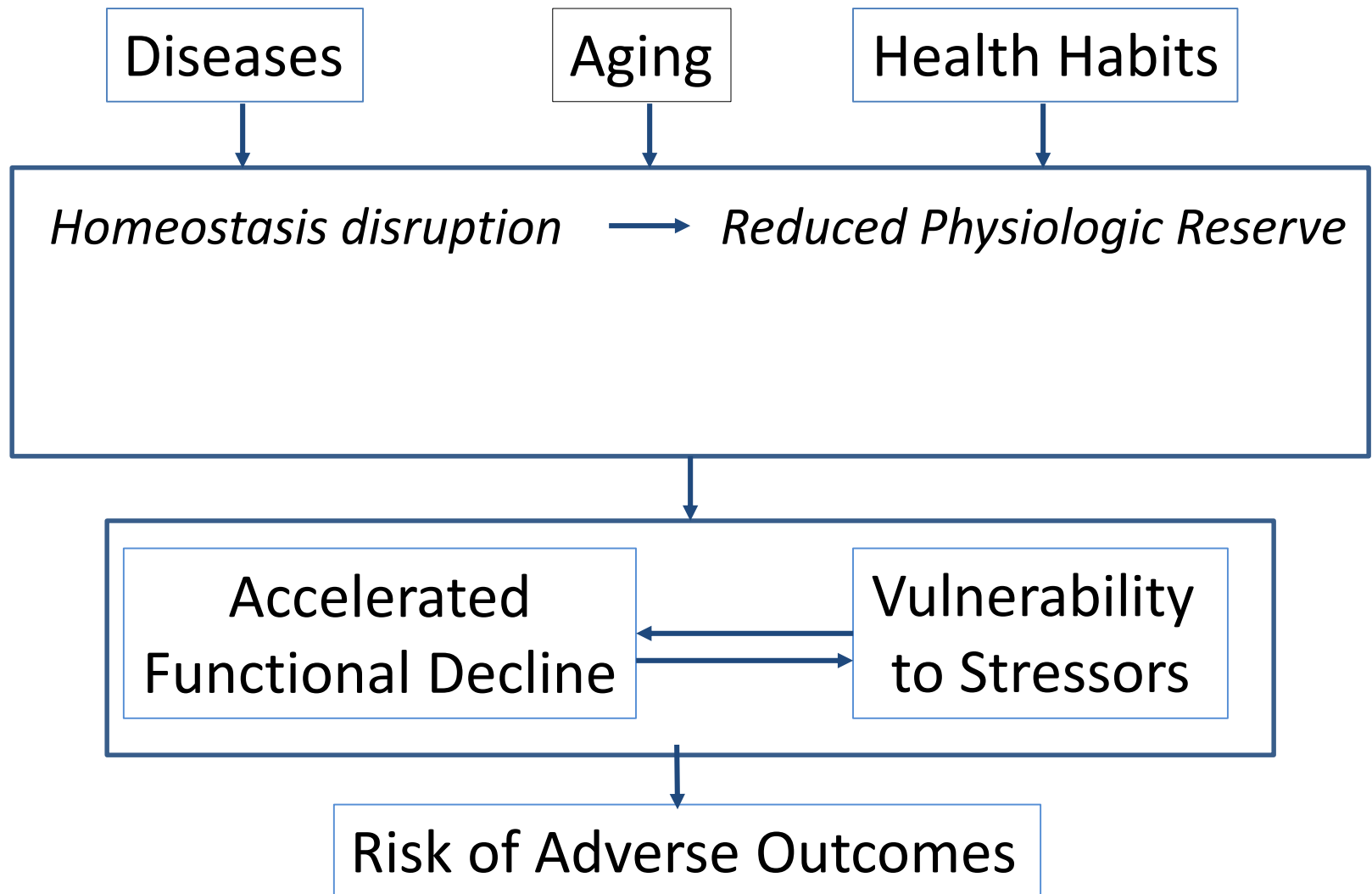
Frailty-related
manifestations

Vulnerability
Frailty Status



Disability &
Other Outcomes

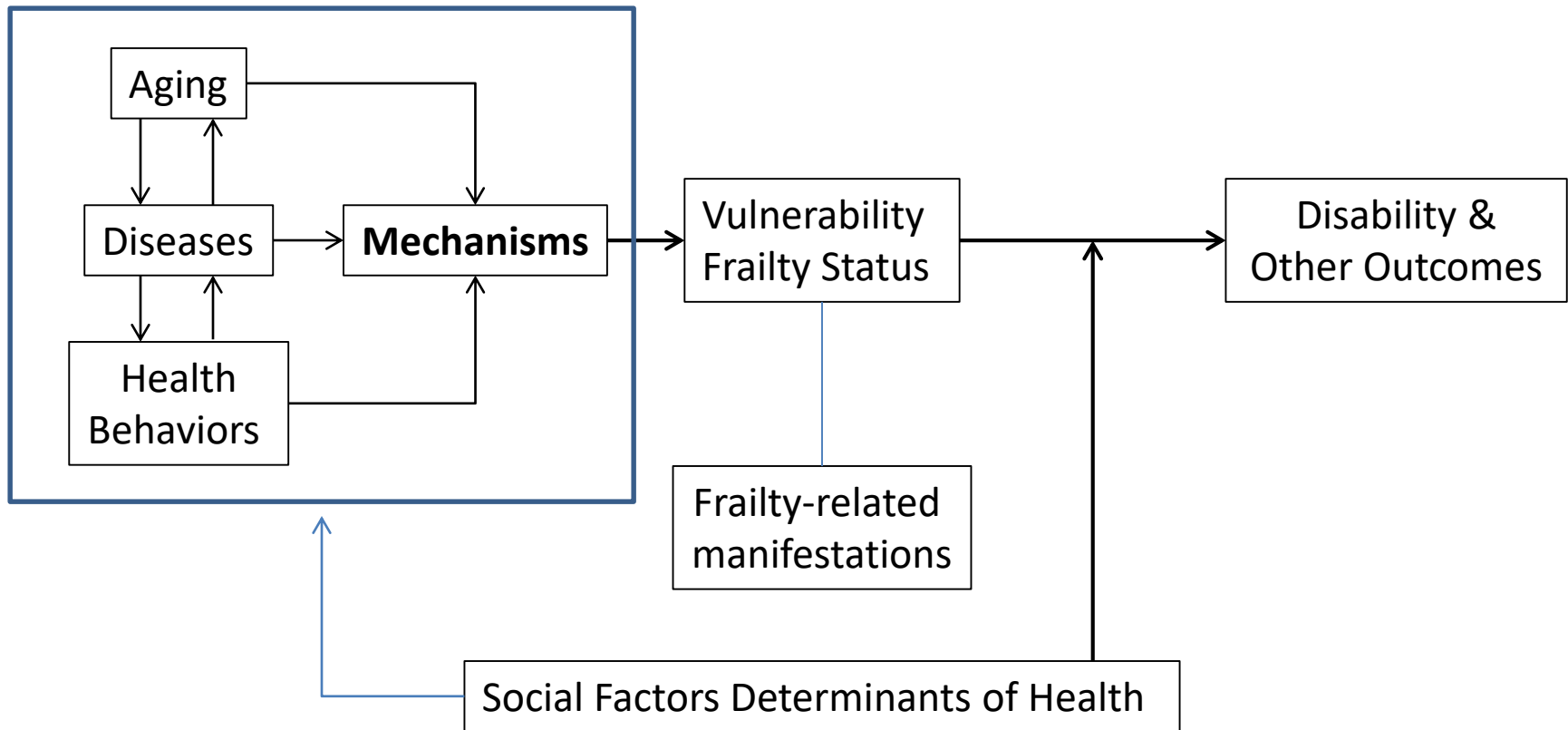
Concept of Frailty



Falls, Disability, NH admission, Hospitalization, Mortality

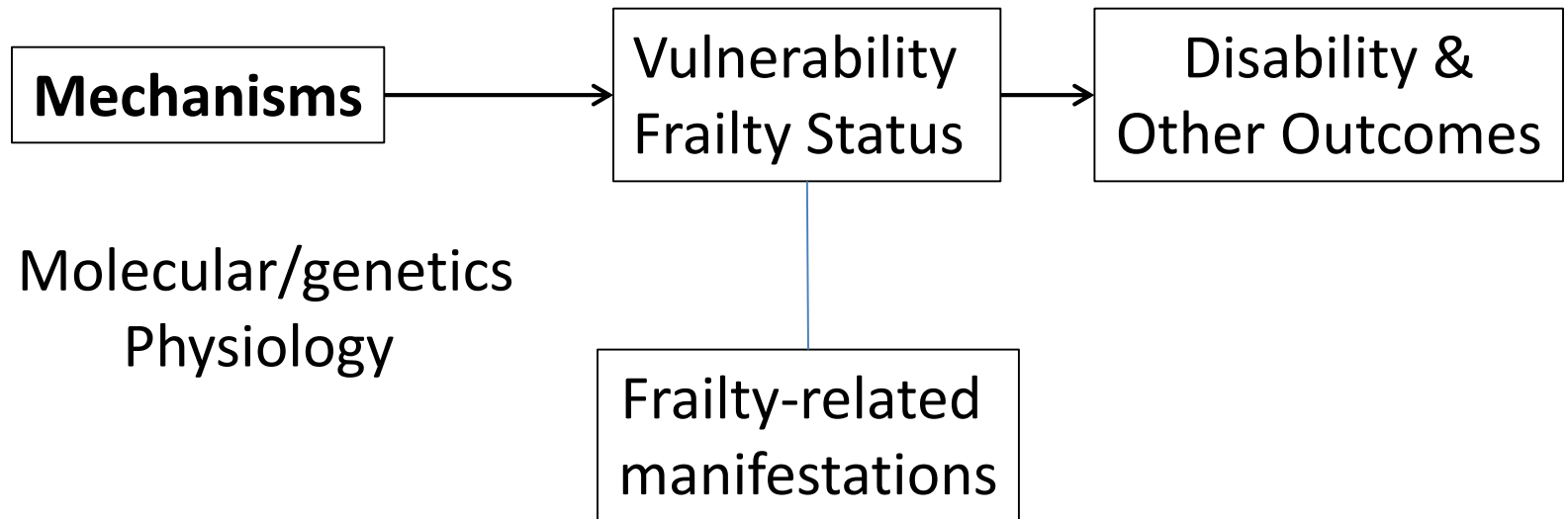
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Frailty as a Unique Geriatric Syndrome

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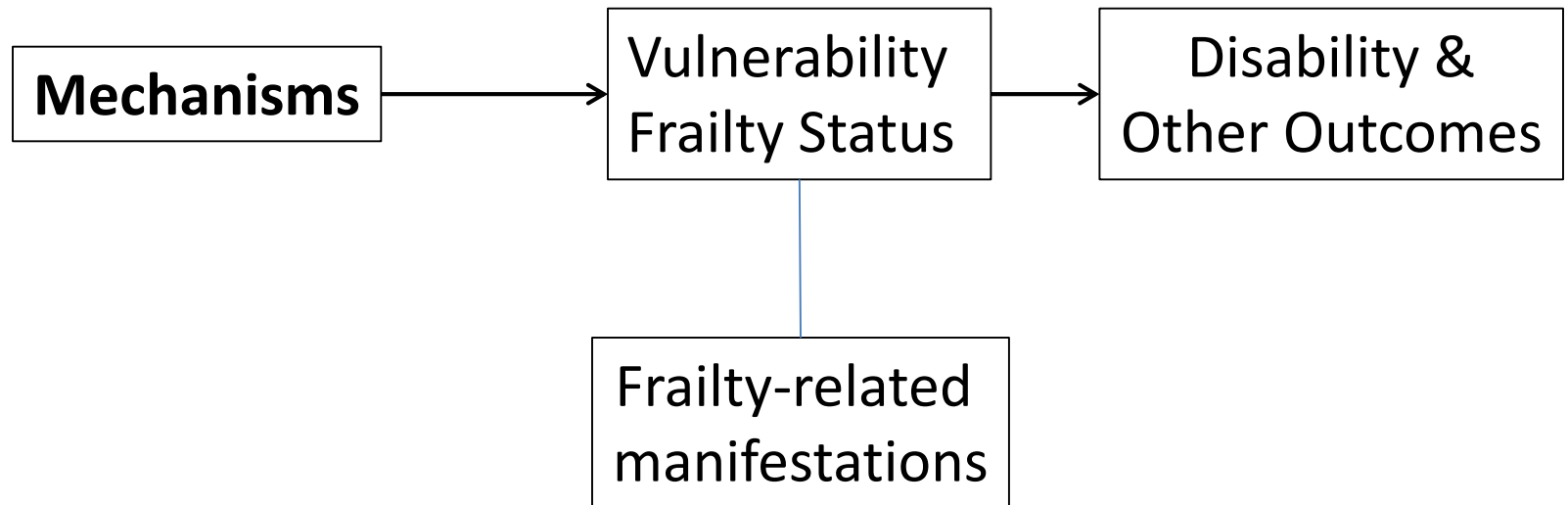


Frailty as a Unique Geriatric Syndrome

- Hypothesis:
 - Driven by genetic/molecular & physiology as driven forces
 - Homeostatic disruption
 - Dysregulation across multiple physiologic systems
 - ical syndrome due to loss of physiological reserve in multiple systems
 - Develops in a stepwise fashion, secondary to stressors such as acute illness or injury
 - Homeostenosis
 - Age-related dysregulation of multiple physiologic systems:
 - Decreased complexity, range and accuracy of system's responsiveness to stress
 - Cumulative declines in reserve across systems, with compromised ability to maintain homeostasis
 - Shifts toward greater and prolonged response to challenges, e.g.:
 - HPA Axis/neuroendocrine stress response system
 - Inflammation
 - Glucose metabolism
 - Cardiohemodynamics
- [Fretwell 1985; Lipsitz & Goldberger 1992]

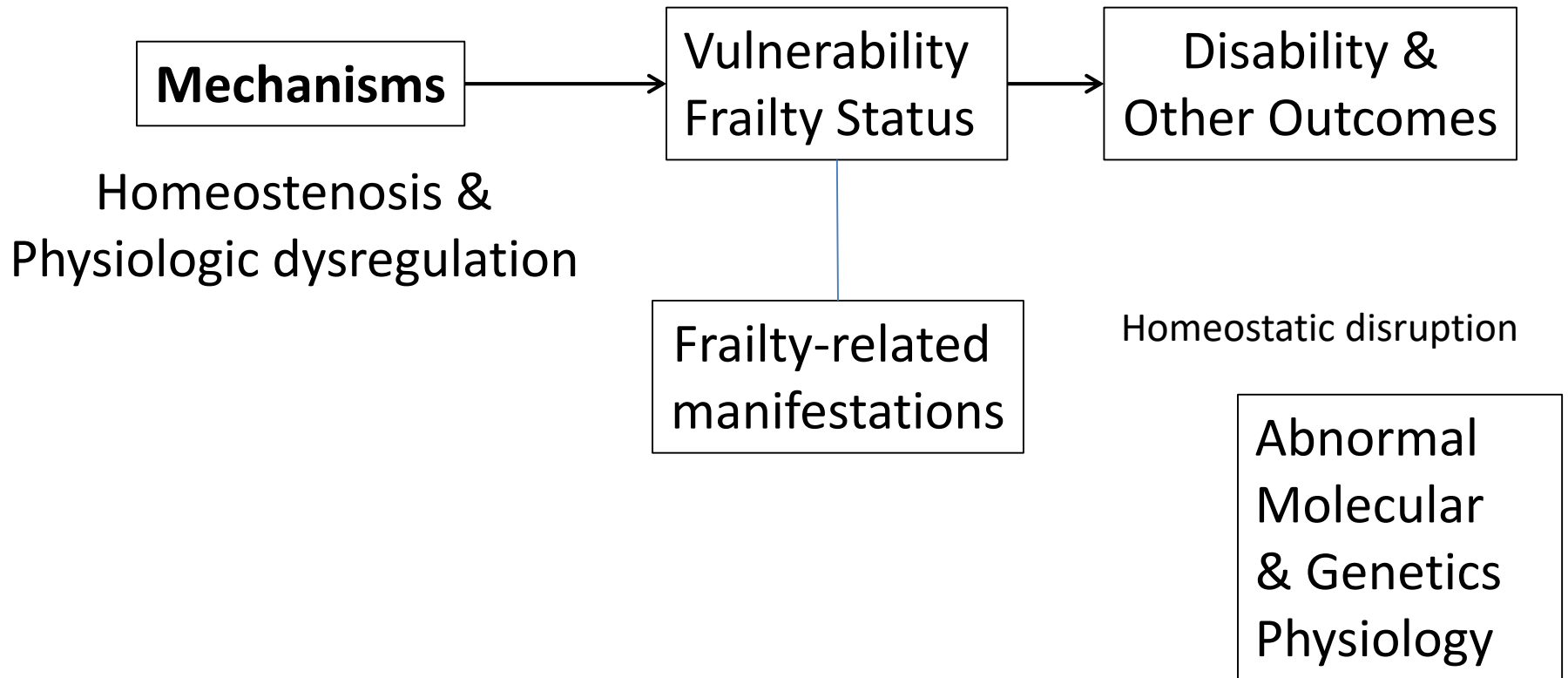
Frailty as a Unique Geriatric Syndrome

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Frailty as a Unique Geriatric Syndrome

- Causal pathway to frailty?



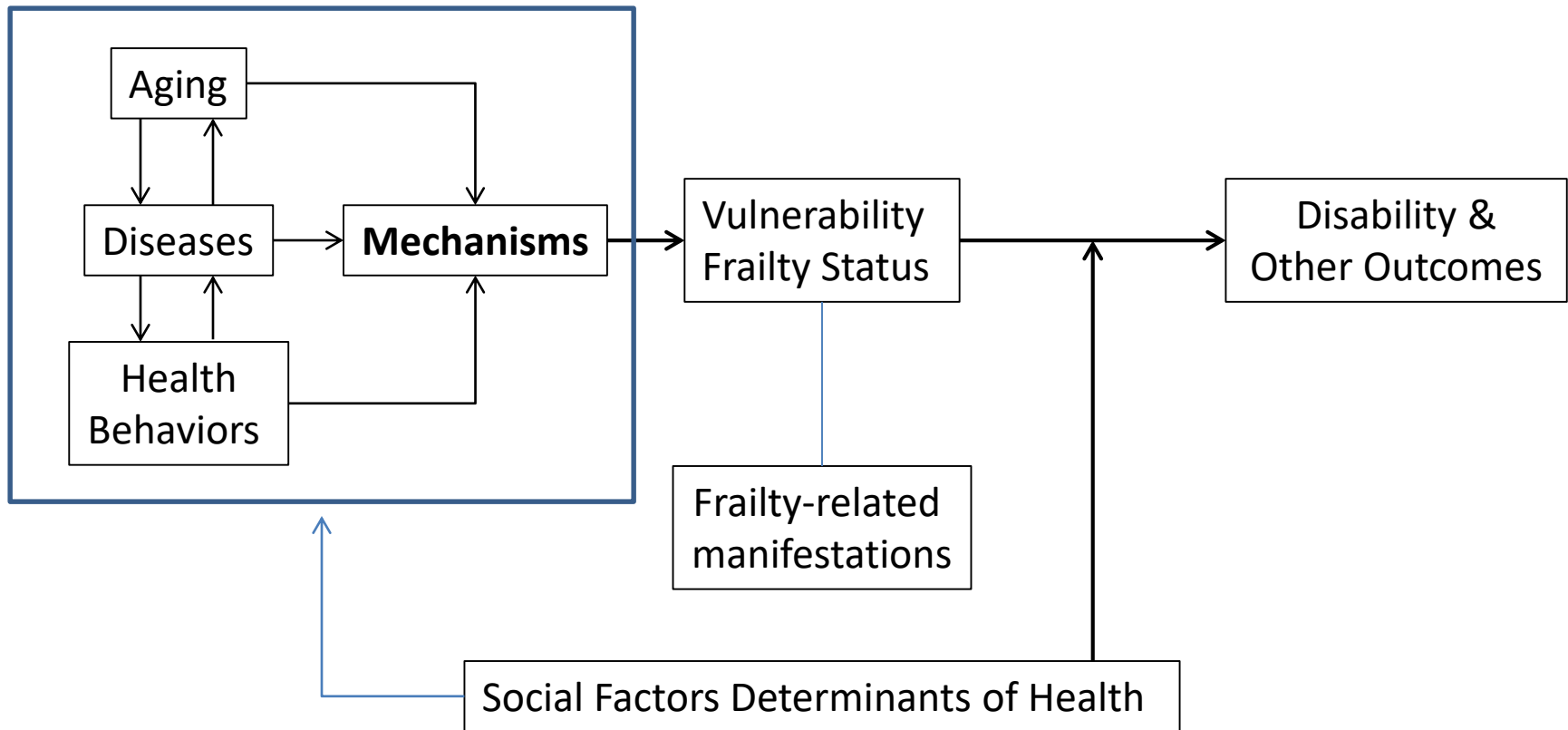
Frailty as a Unique Geriatric Syndrome

- Hypothesis:
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[Fretwell 1985; Lipsitz & Goldberger 1992]

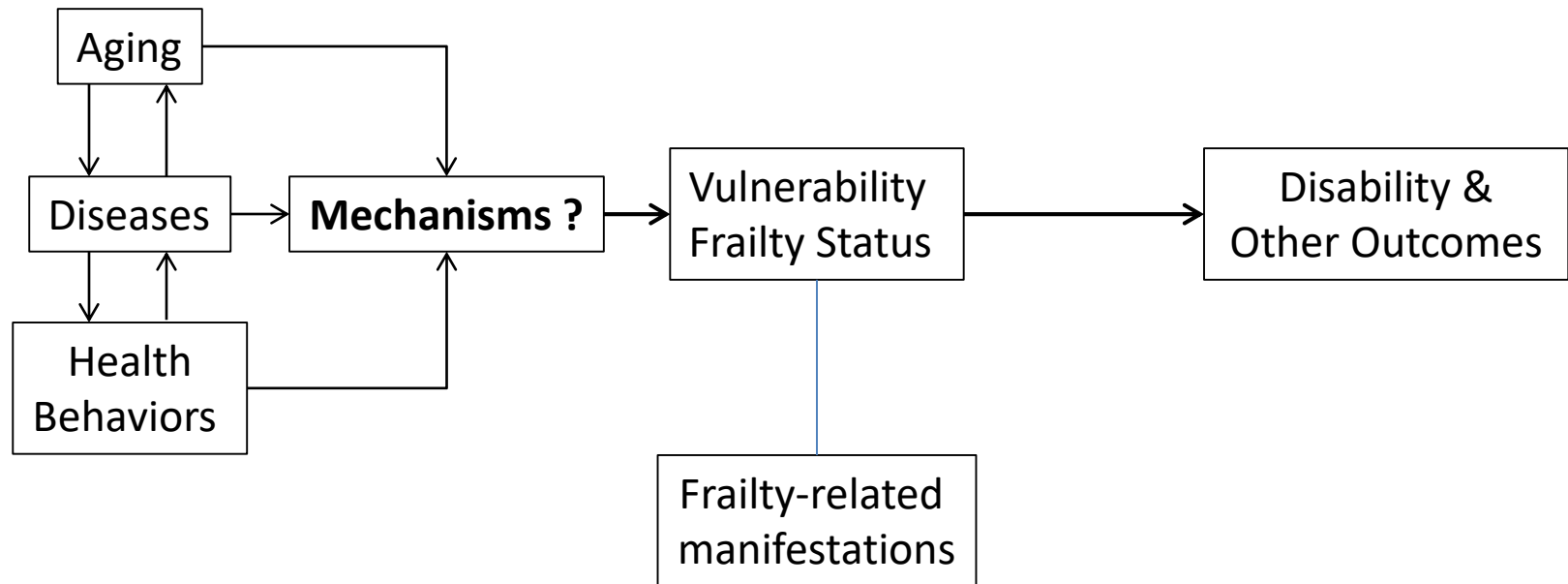
Frailty as a Unique Geriatric Syndrome

- Causal pathway to frailty?

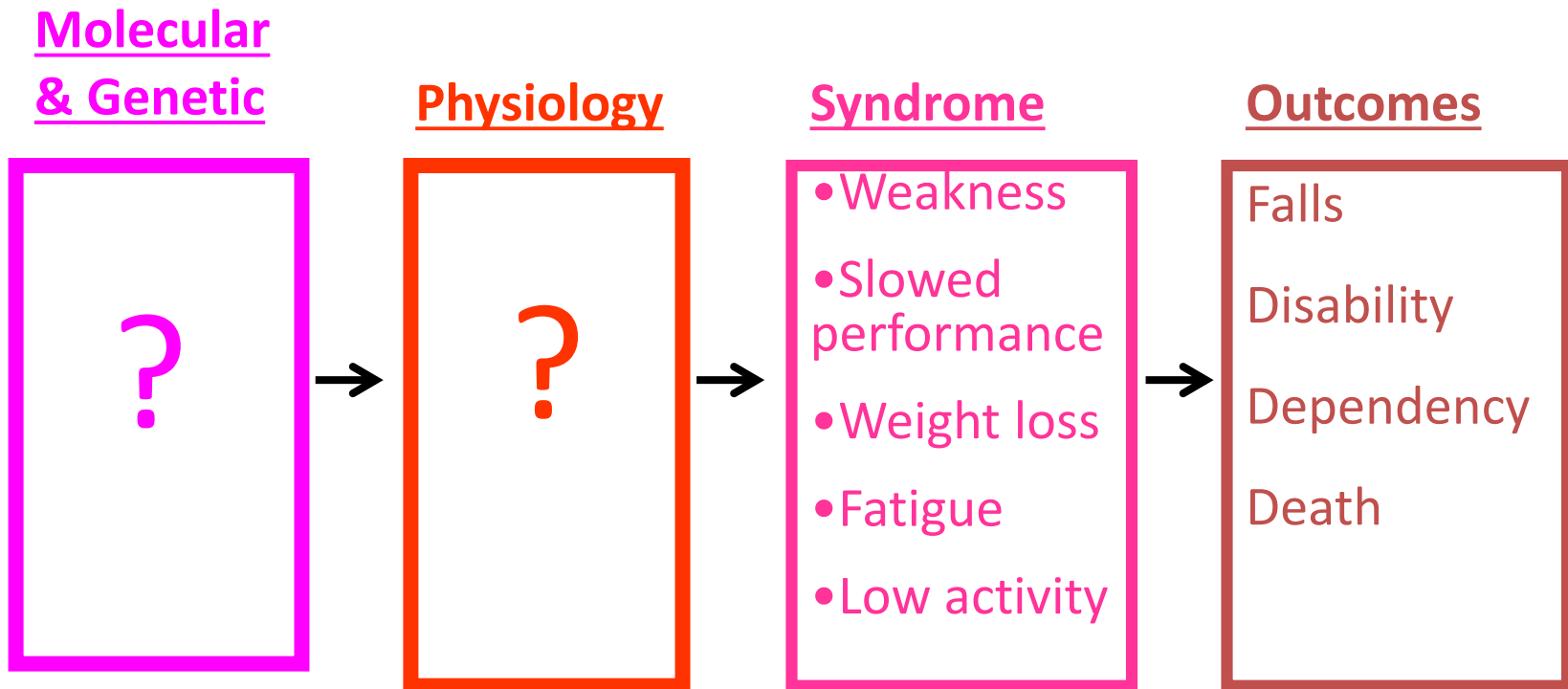


Frailty as a Unique Geriatric Syndrome

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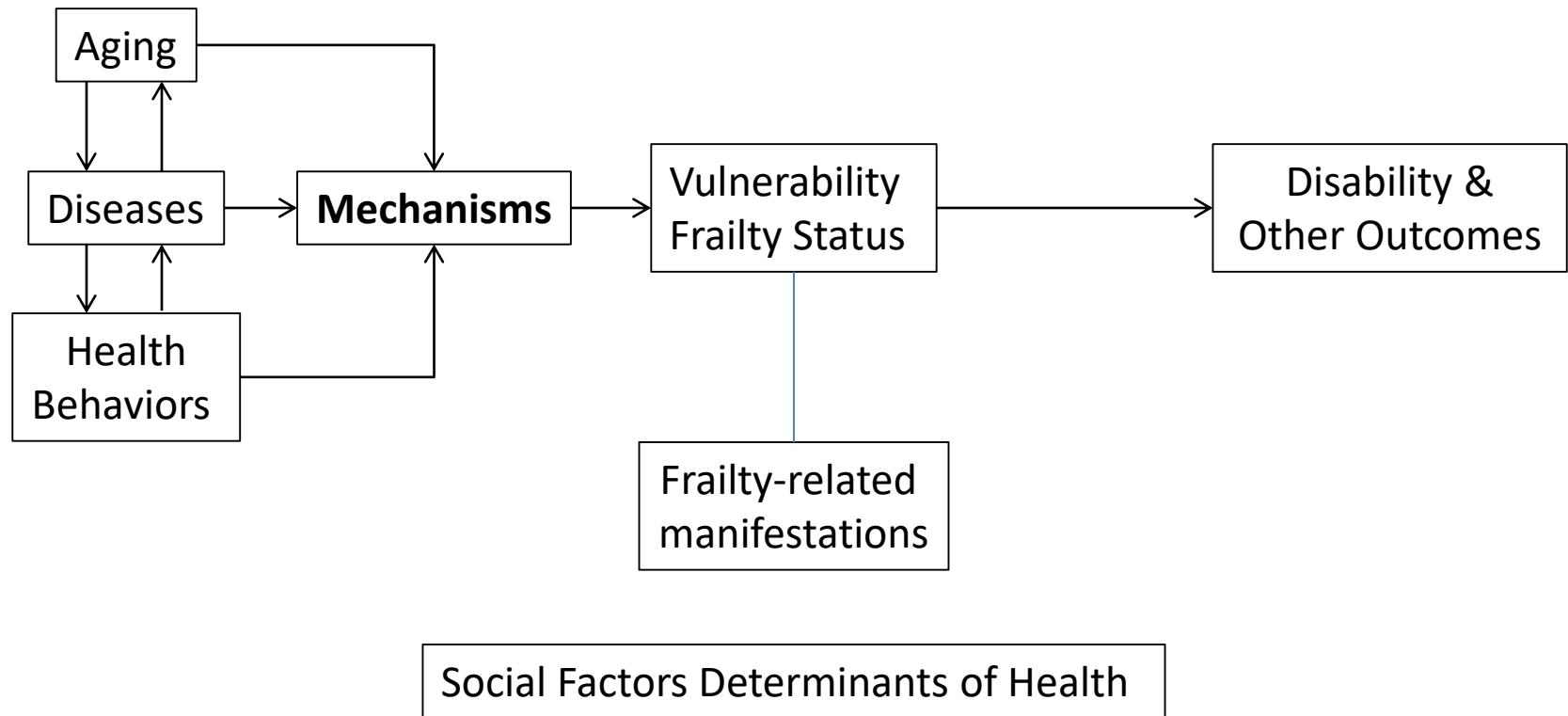
Causal Pathway for Frailty



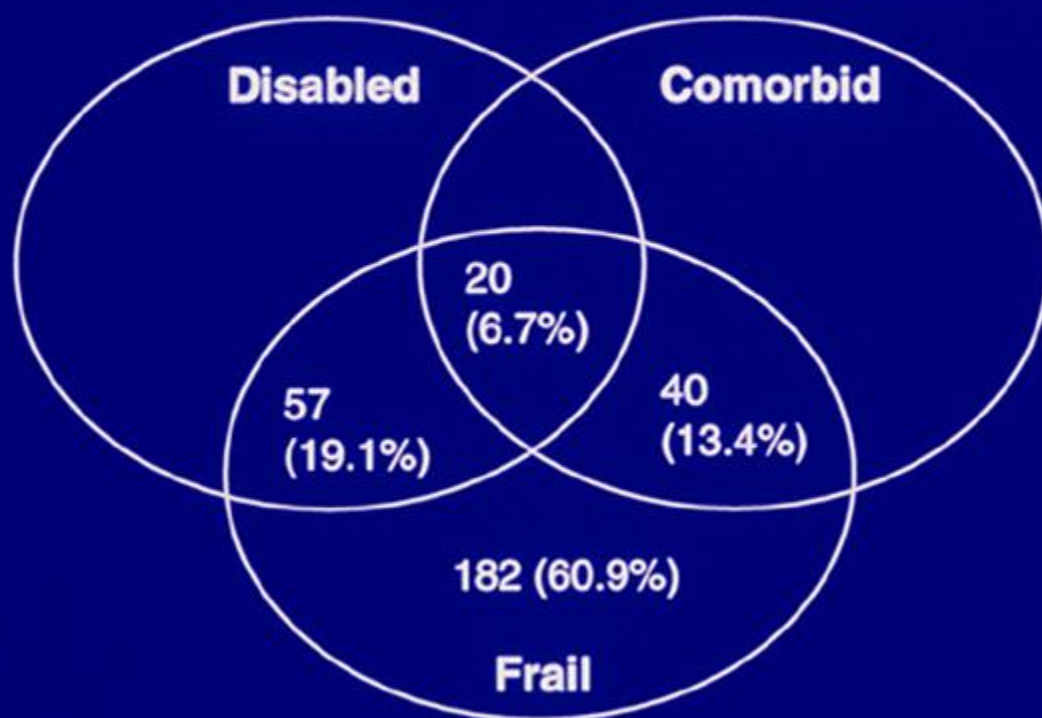
Fried and Walston, Principles of Geriatric Medicine and Gerontology (Wm Hazzard, Ed.) 1998, *Adapted*.

Frailty as a Unique Geriatric Syndrome

- Causal pathway to frailty?



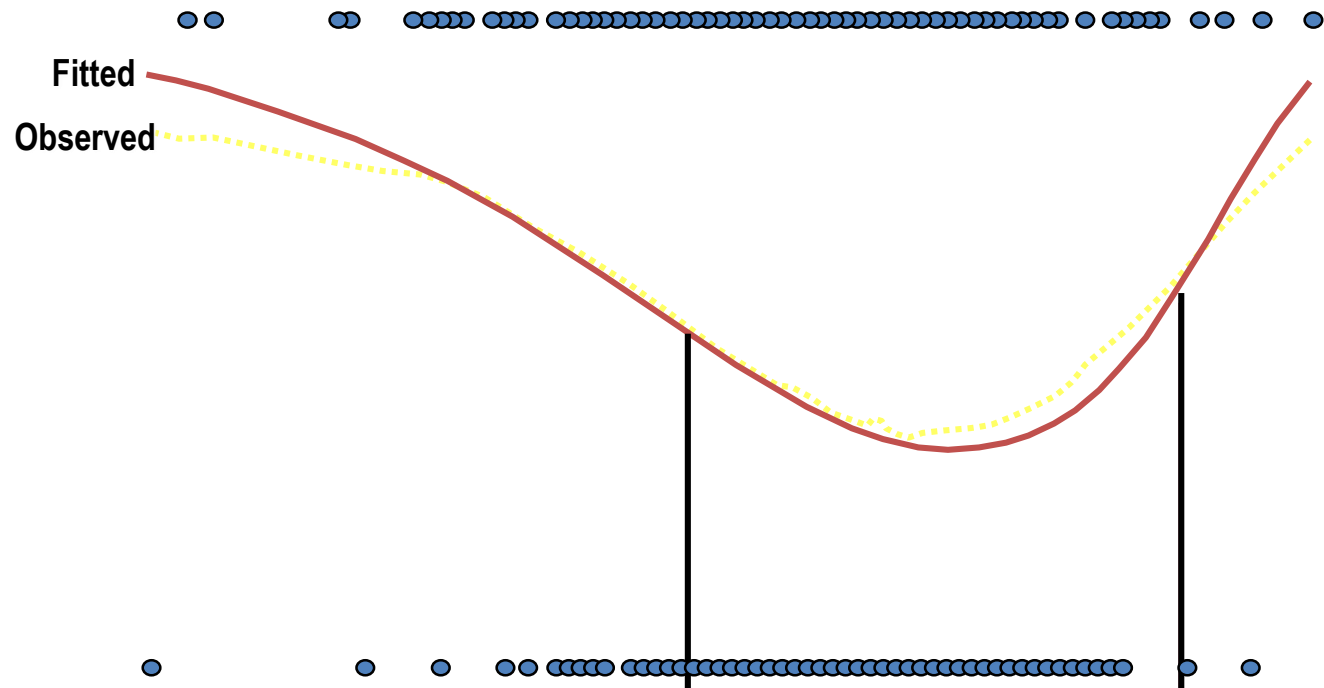
Frailty, Disability and Comorbidity in CHS



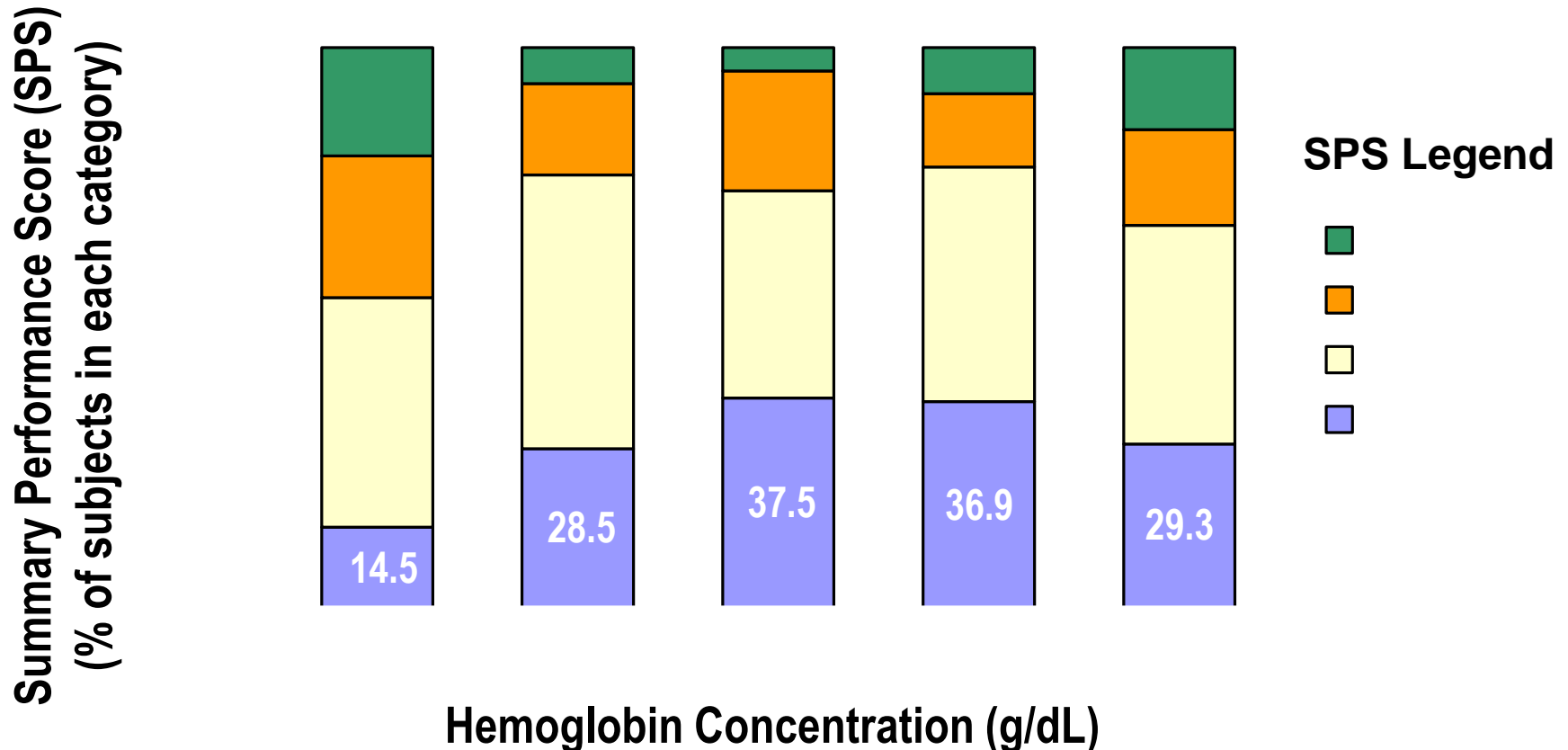
Pathway to disability

- Disaggregate frailty and preclinical disability
 - Frailty a marker of aggregate declines in physiologic reserve and vulnerability to an array of adverse health outcomes, including disability
 - Preclinical Disability the response of the individual to functional decrements due to underlying health changes – compensation to preserve function, delay disability.
 - Both may be outcomes of comorbidity

Scatterplot Displaying the Relationship Between Self-Reported Mobility Difficulty (Walking ¼ Mile or Climbing Up 10 steps)

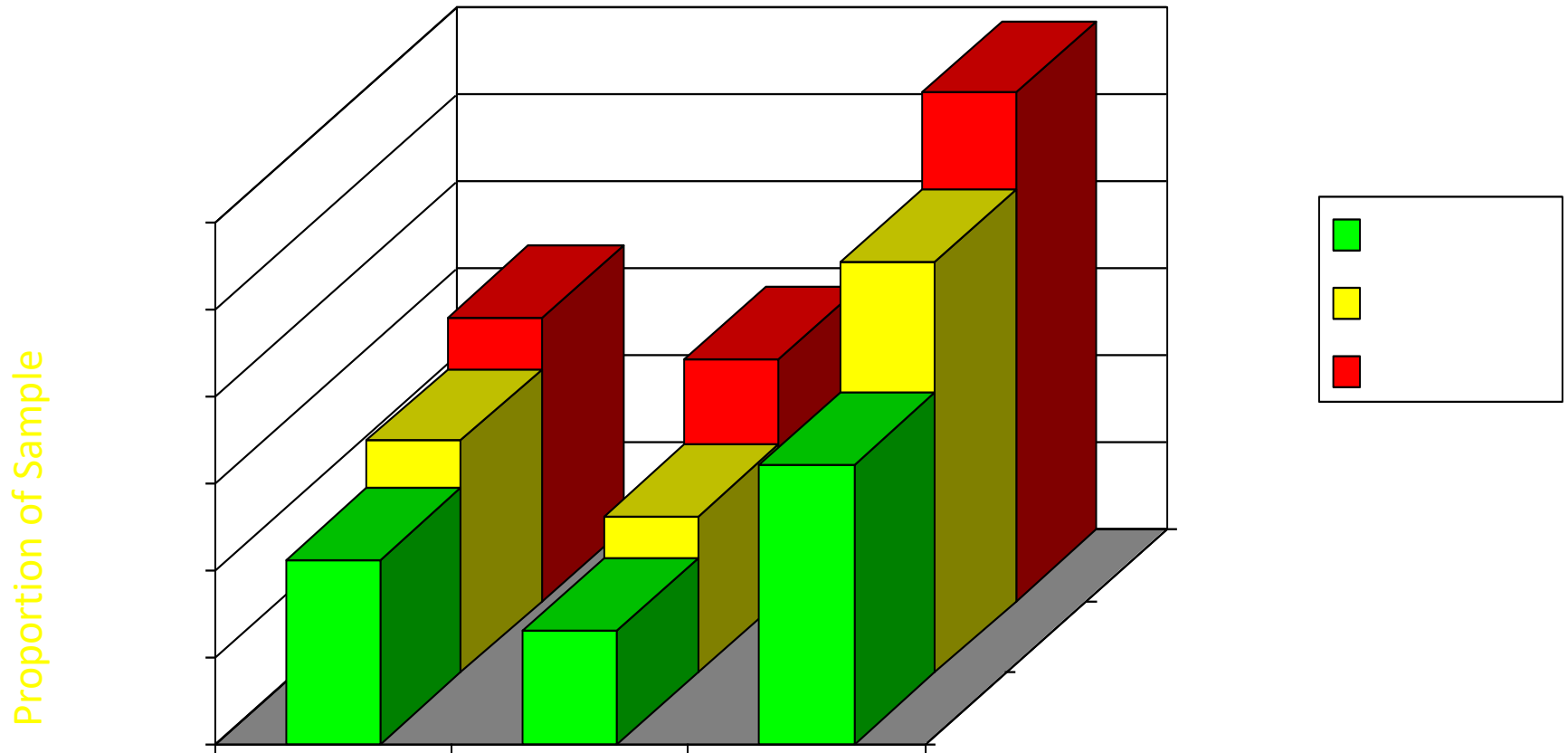


Relation Between Categories of Lower-Extremity Summary Performance Score (SPS) and Hb



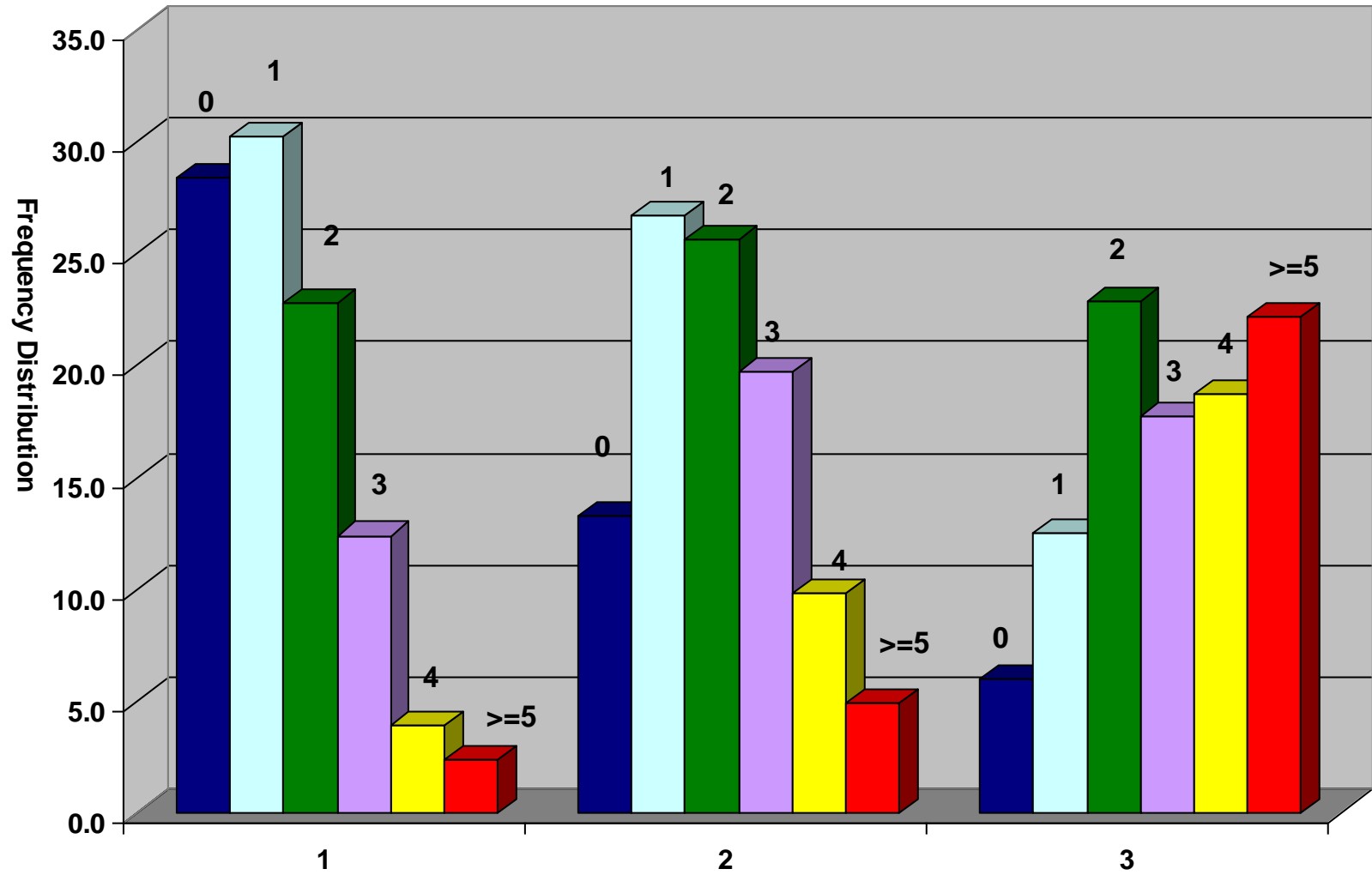
SPS → Higher scores indicate better performance/functional status.
Indicated is the proportion of subjects in the best SPS category: 10–12

Prevalence of Frailty for 3 Blood Test Abnormalities in 70-79 year olds in WHAS I and II



System	Measure	Cutoff	Non-Frail	Pre-Frail	Frail	Overall
			N=284	N=331	N=90	705
Anemia	Hemoglobin	<12 gm/dL	10.1	13.2	27.5	13.4
Inflammation	IL-6	>3.7 pg/mL	27.1	33.4	35.2	30.7
	CRP	>7.5 mg/L	19.5	24.3	34.1	23.3
Endocrine	IGF-1	<74.3 ng/mL	14	18.8	26.9	17.7
Glucose Tolerance	GHB	>8.6 % for 673A	10.3	20.5	19.8	15.8
		>7.1 % for 673B				
Immune Function	Lymphocyte	<18%	9.3	6.5	15.3	8.7
Sarcopenia	AMA	Bottom Quartile	12.1	27.4	59.2	24.8
Fine Motor Speed	Purdue Pegboard	Bottom Quartile	14.5	27.1	51.8	24.6
Hormone	DHEA-S	< 0.215 mcg/ML	1.9	5.6	18	5.4
Nutrient	25-OH Vit. D	<30 nmol/L	17.9	24.1	35.7	22.7
	Folate	<5 ng/mL				
	B12	<300 pg/mL				
	Alpha-tocopherol	<11.6 umol/L				
	Total Carotenoids	<0.45 umol/L				
	(>=2)					
	Albumin	<3.75 gm/dL	3.3	8.5	21.4	7.6

Combined WHAS I and WHAS II (Age 70-79)



Hypothesized Pathway to Frailty and Loss of Independence in Older Adults

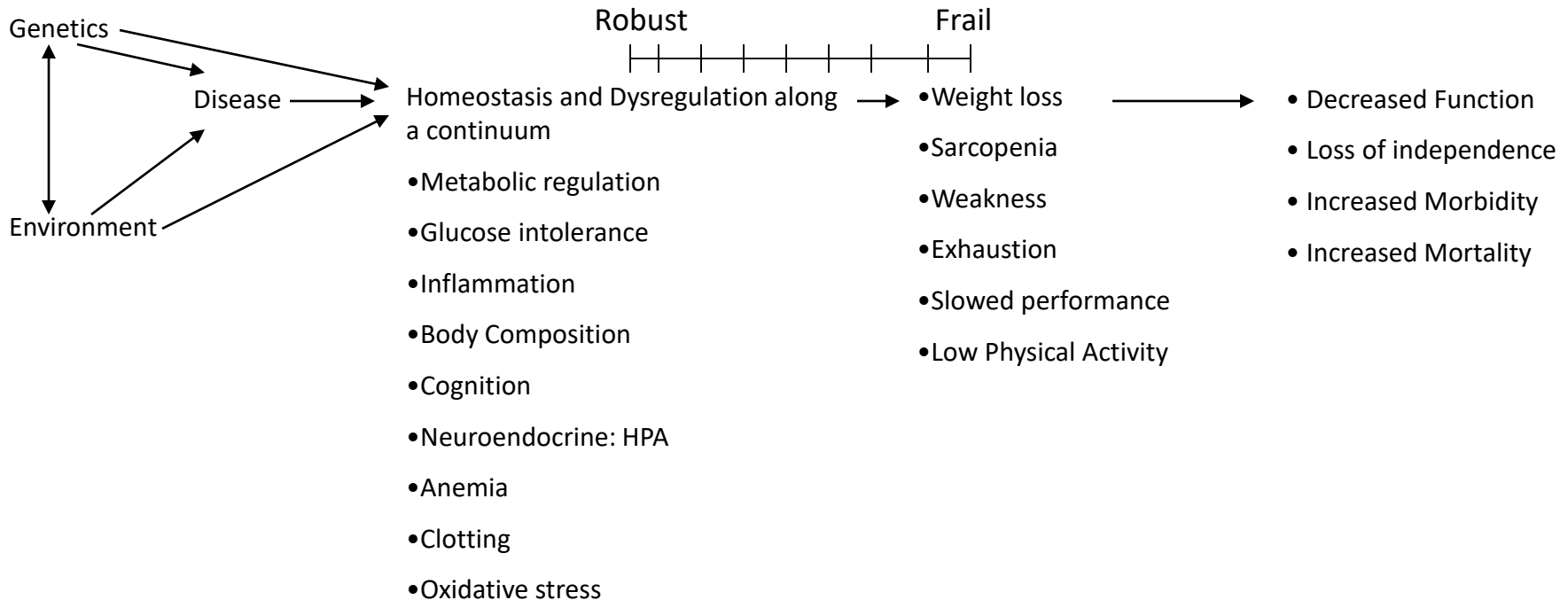
Ultimate Causes

Subclinical Components and Mechanisms

Clinically Observable Syndrome

Distal Outcomes

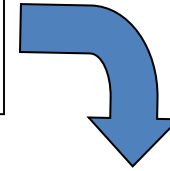
RESILIENCY



Natural History of Investigation

7/1. The Genesis and Rationale:

Clinical Problem



2. Conceptual Framework:

Population-based and Clinical Evidence



3. Phenotype:

Clinically observable syndrome

- Population-based evidence
- Modifiable pathways



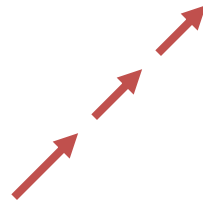
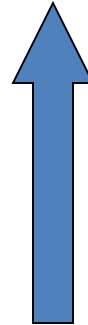
4. Converging Literature:

Hypotheses development

- Physiology: subclinical components and mechanisms
- Biology: Ultimate cause



Clinical Trials



6. Ultimate Causes:

Genetics – Environment

Laboratory ↔ Populations

-- Modifiable Pathways --



5. Subclinical Components and Mechanisms:

Hypothesis testing;

Modifiable Pathways

Population ↔ Laboratory

Outcomes

- Similar to disability in terms of mortality and healthcare utilization
- Bidirectional associations
- Should disability be a part of it?
- Differences and similarities

- frailty phenotype and the frailty index

Risk factors for Frailty:

Selected examples of Chronic Diseases

- Age-related chronic diseases or conditions
- Cardiovascular disease
- Diabetes
- Osteoarthritis
- Obesity
- Depression
- eGFR
- Subclinical diseases
- Health Habits
- Low physical activity
- Diet – proteic-caloric
- Alcohol excessive

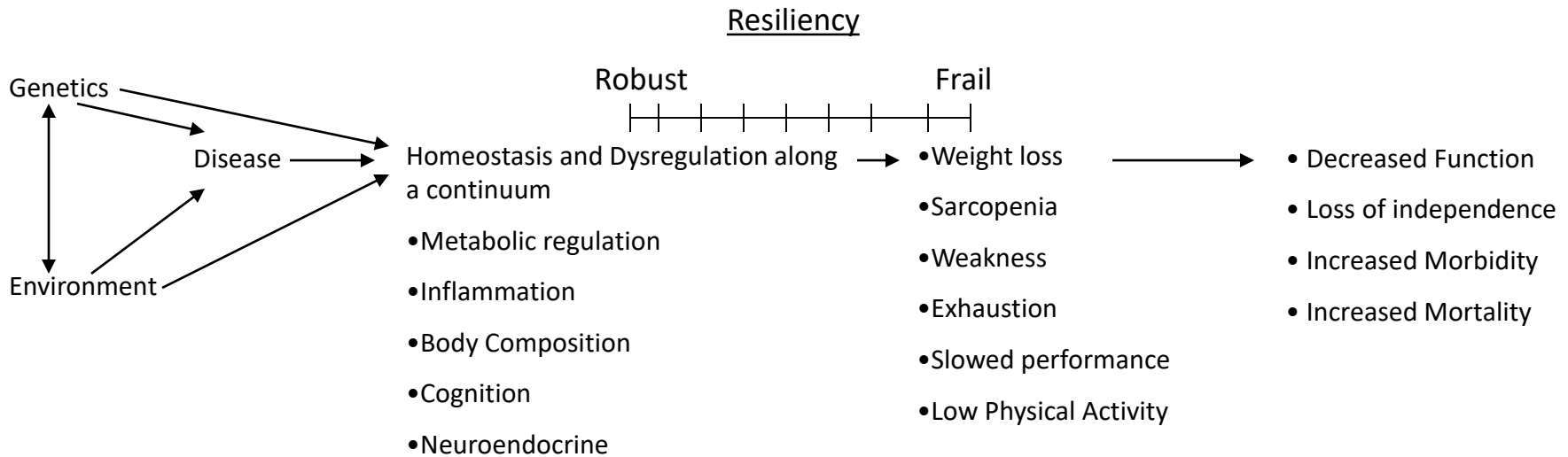
Hypothesized Pathway to Frailty and Loss of Independence in Older Adults

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Clinically Observable Syndrome

Distal Outcomes



FRAILITY IN OLDER ADULTS

- Marker of health status deficits that accumulate over life to indicate overall risk?
- Actual entity with a common etiology that offers the basis for prevention?
- Is it a cause or a marker?
- Thus, potentially preventable

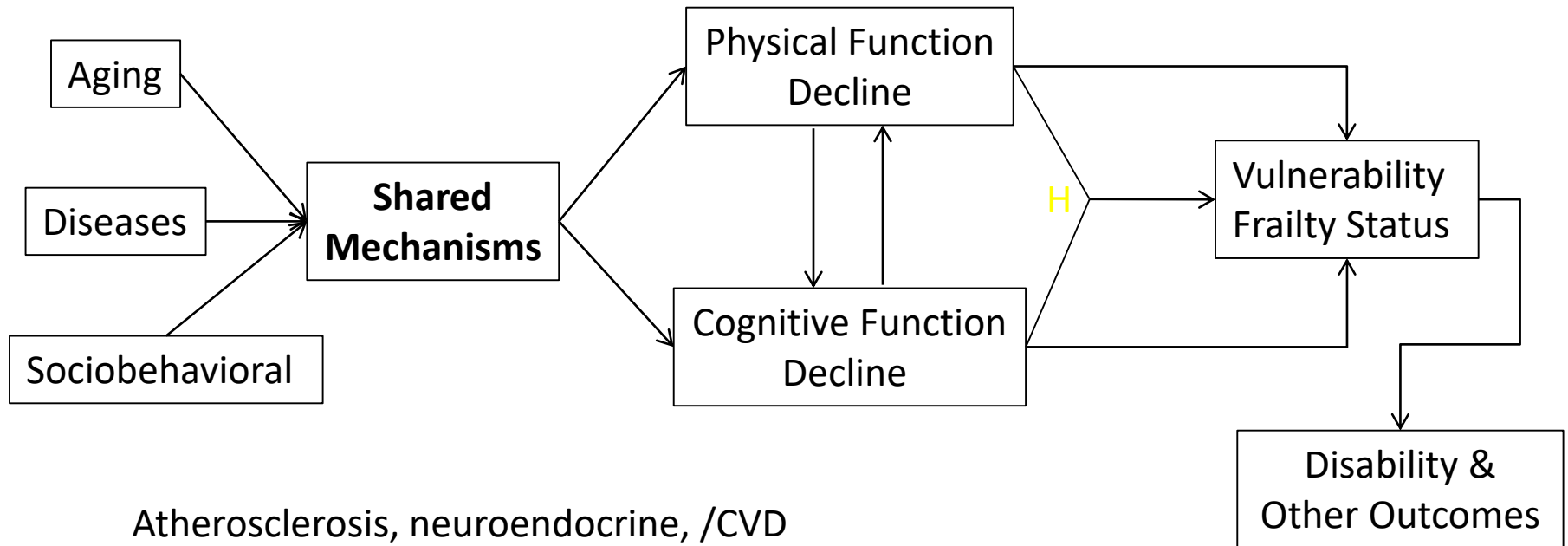
Mechanisms of frailty: systems biology

- Multisystem dysregulation and its association with frailty: aggregate effects and delicate balancing of systems essential to homeostasis
- Define relationships within and between levels:
 - Clinical presentation
 - Physiologic dysregulation
 - Cellular dysregulation
 - Molecular/genetic

Selected Debated Issues :

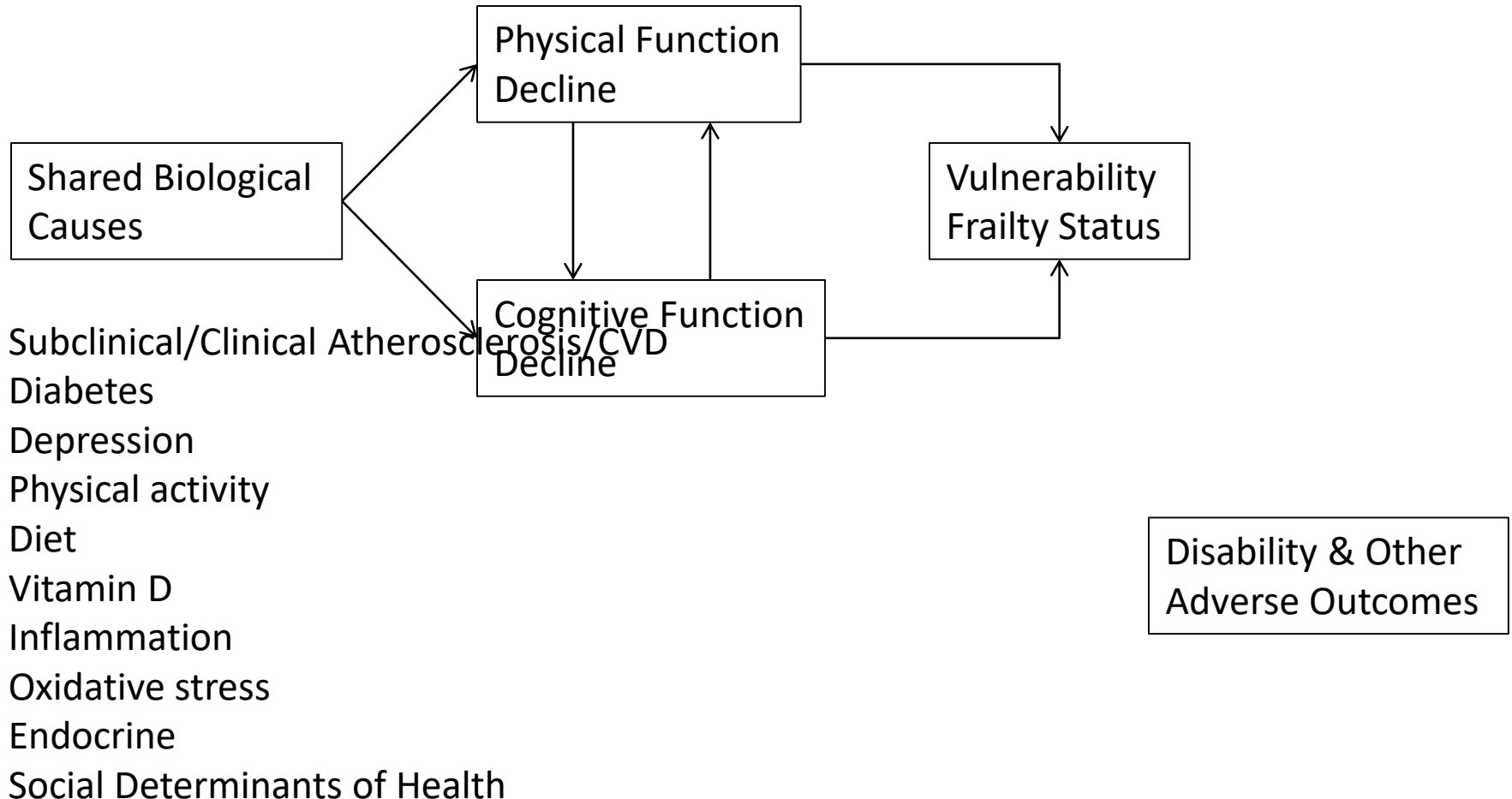
Cognition in the definition of frailty?

- Biological Plausibility perspective
 - Common underlying pathophysiologic basis of which physical and cognitive decline are manifestations?



Atherosclerosis, neuroendocrine, /CVD
Diabetes
Depression
Physical activity

Additional Aspects: Frailty and Cognition



Frailty is more than its phenotype

- Marker of other things

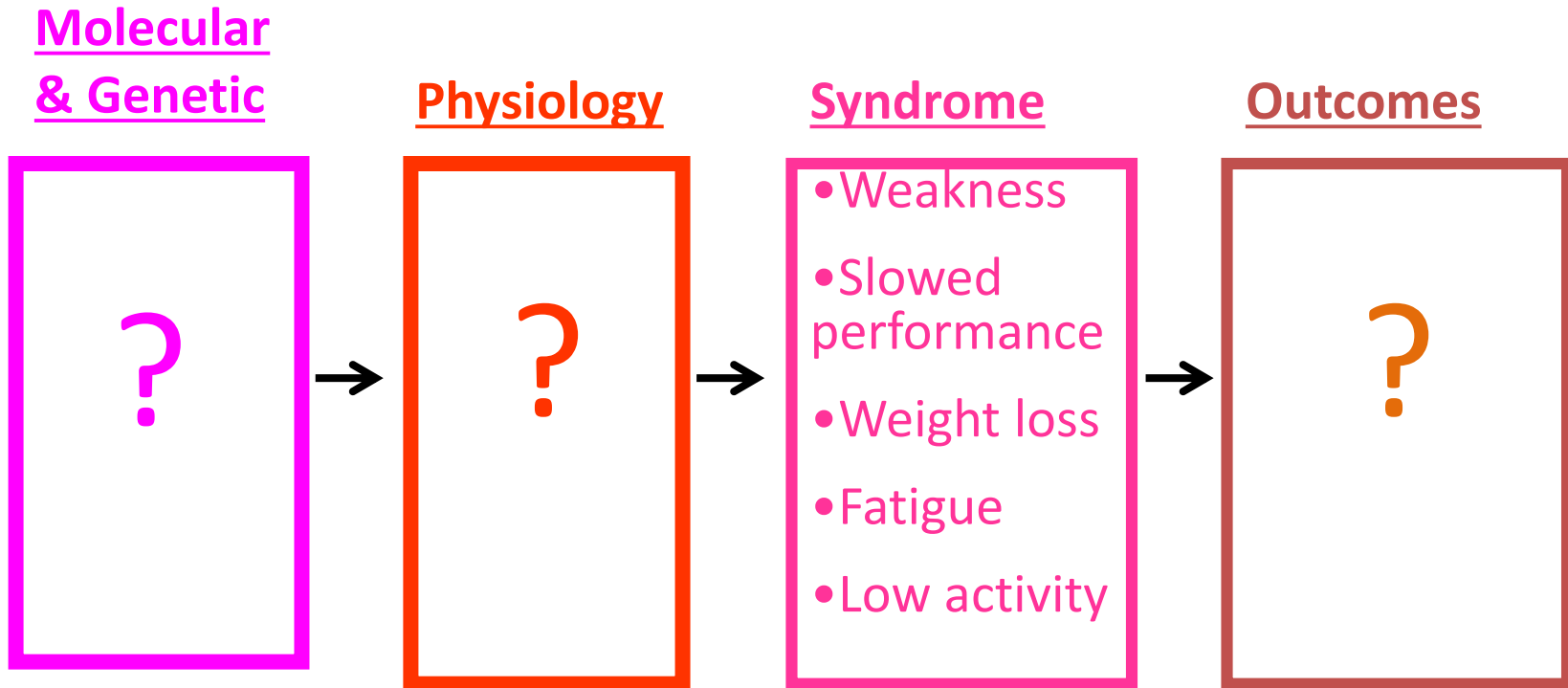
- Unique value

- Falls: value

Next Steps: The Underlying

Etiology of Frailty Syndrome

Causal Pathway for Frailty



Fried and Walston, Principles of Geriatric Medicine and Gerontology (Wm Hazzard, Ed.) 1998.

Is Frailty More than an Aggregate of Measures Indicating Vulnerability?

V

Vulnerability

Adverse Outcomes

Frailty – Many Questions

- Is Frailty more than its phenotype (more than just vulnerability?), is there an Underlying Etiology
- Marker of other things
- Unique value
- Falls: value

Is Frailty More than a Phenotype/Aggregate of Measures Indicating Vulnerability?

Implications for assessment of frailty status

Adverse Outcomes

No

Main Goal: Risk Prediction

All possible variables that maximize risk prediction

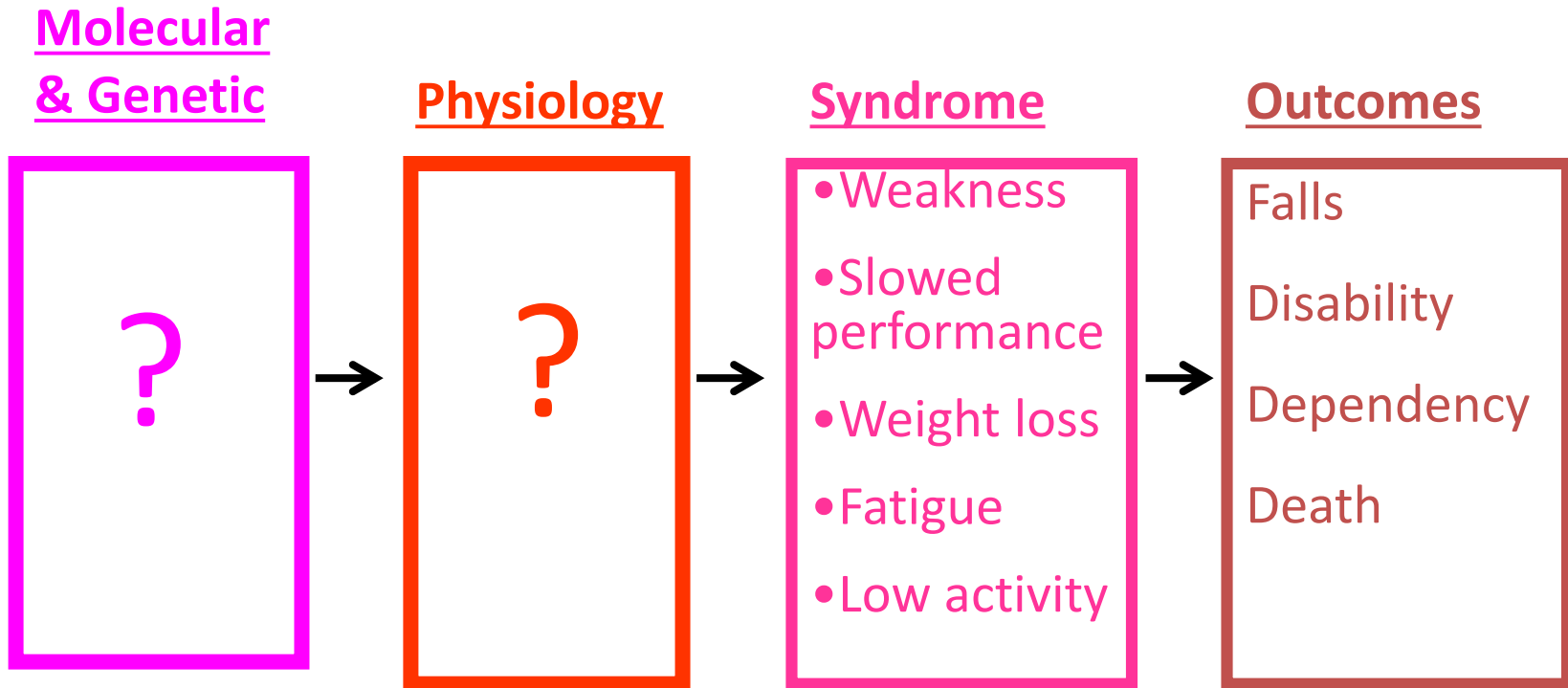
V

Vulnerability

Variables do not need to be thought of as “causal”

Variables do not need to be correlated

Causal Pathway for Frailty



Fried and Walston, Principles of Geriatric Medicine and Gerontology (Wm Hazzard, Ed.) 1998.

Frailty

- Consensus:
- Has been a dominant theme
- Philosophically: reason to be a physician
- Embrace complexity
- Disease itself is not enough
- Focus on function
- Academically: publications graph
- Leo's textbook, Cecil/Harrison, Hazard, Pether ...
- Increasing interest in other disciplines

Epidemiology of Frailty: Selected Aspects

- Prevalence

Phenotype of frailty

- Prevalent in community-dwelling older adults
- Aggregate syndrome associated with high risk for adverse outcomes, adjusting for diseases
- Predictor of disability; not synonymous
- Potential method for screening; now validated in national and international working groups, 2002.

To specialize in conducting aging research is ...

- To embrace the challenge of dealing with health status heterogeneity and its complexities
 - Thinking about it every minute, from study conception & design, to data analysis & reporting
- To think differently than the paradigm taught in Epi 1
 - Disease as risk factors for outcomes (e.g., frailty)
- To understand that this segment of the population has unique, special demands, and to be happy about spending additional and substantial amount of effort to ethically match these demands, and accomplish the scientific pursuit
 - Thus, when conducting research in a special group such as the older population, “special” gerontological approaches are necessary to deal with a series of specific issues, which will be discussed in this talk.

FRAILTY INDEX

- “Shrinking”- involuntary weight loss >10%
- Weakness – grip strength <20th pctile
- Slowness – walking speed <20th pctile
- Exhaustion – CES-Depression Scale mod.
- Decreased physical activity – Minnesota Leisure Time Activity questionnaire –
 - bottom 20th pctile of calculated Kcal

NUMBER OF OTHER MEASURES OF FRAILTY

- VES
- Pra
- Alguma outra “Shrinking”- involuntary weight loss >10%
- Weakness – grip strength <20th pctile
- Slowness – walking speed <20th pctile
- Exhaustion – CES-Depression Scale mod.
- Decreased physical activity – Minnesota Leisure Time Activity questionnaire –
 - bottom 20th pctile of calculated Kcal
- Jody Segal

- 3 major vertents
 - Own pathogenesis
 - Marker
-
- Health records

Using the phenotype advanced knowledge about the natural history of frailty

- Outcomes
- Transient
- Early manifestations
- Risk factors
- Compare to Andreas Stuck

Selected Aspects of the Epidemiology of Frailty

- Prevalence
- Risk Factor
- Natural History
- Biomarkers
- Opportunities for prevention

Mechanisms for Frailty: Molecular & Genetics & Physiology

- Molecular & Genetics
- Mitochondrial dysfunction
- Epigenetics
- Senescence
- Autophagy
- Physiology
- Exaggerated stress response
- Chronic activation of inflammation pathways
- Telomere dysfunction
- Immuno dysfunction
- Autonomic dysfunction

Risk Factors for Frailty: Molecular & Genetics

- Mitochondrial dysfunction
- Autophagy
- Oxidative stress
- Inflammation
- Telomere dysfunction
- Immuno dysfunction
- Autonomic dysfunction
- Loss parasympathetic, increased sympathetic
- Neuroendocrine

Physiologic impairments in frailty Association of abnormal levels in multiple physiological systems with frailty

- Sarcopenia
- Inflammation
- Decreased heart rate variability
- Altered clotting processes
- Altered insulin resistance
- Anemia
- Altered neuroendocrine axis:
 - cortisol response to stress

Evidence to date: Biomediators associated with frailty syndrome

- Independent: IGF1, IL-6, anemia, clotting factors, insulin resistance, undernutrition
- Pairwise: IGF1 * IL-6
- Parallel: DHEAS, IGF1, IL-6

- Muscle
- Inflammation
- Hormones
- Vitamin D
- Anemia
- Comprehensive geriatric management

Hypothesized Pathway to Frailty and Loss of Independence in Older Adults

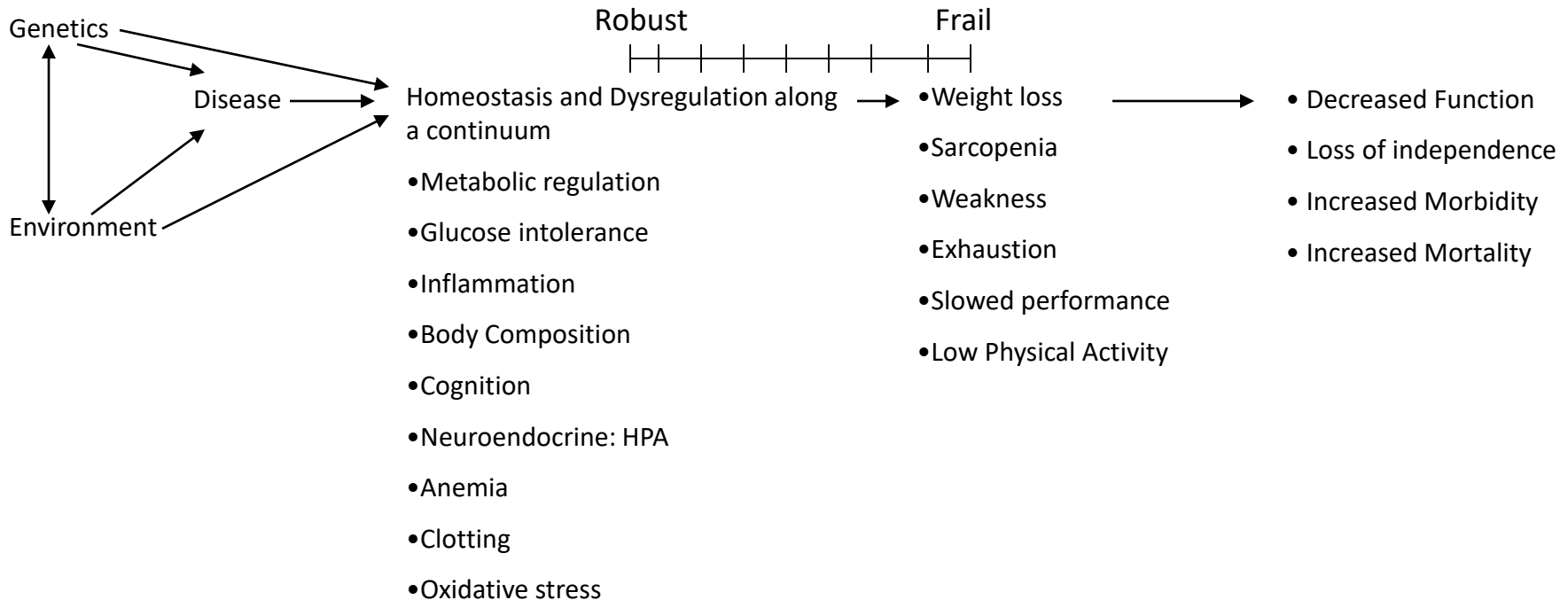
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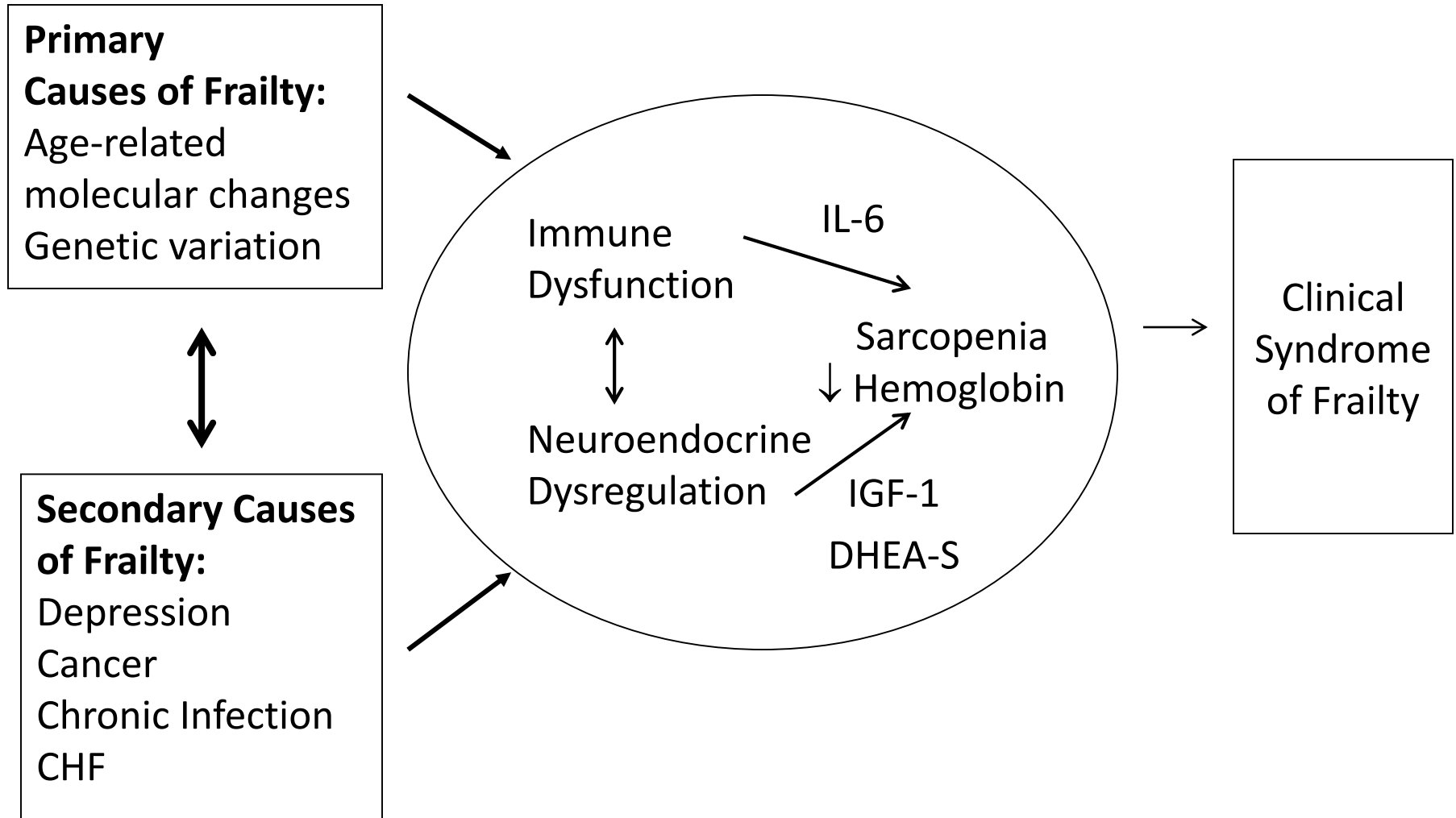
Clinically Observable Syndrome

Distal Outcomes

RESILIENCY



Causal Pathway 2003



FRAILITY IN OLDER ADULTS

- Much progress
- Conceptual frameworks
- Operational definitions
- Descriptive epidemiology
- Increased awareness
- Even outside discipline
- Worldwide collaborations specific on frailty
- Still lots of questions
- Conceptualization
- Methods
- Groundwork for next steps
- Frailty clinic – Toulouse
- Frailomics
- Rockwood's
- Hopkins Pepper Center

Conclusion

- Geriatrics management approaches
- Emphasis on functional decline and quality of life
- Competing issues
- Multiple morbidities
- Polypharmacy
- Life expectancy limitations
- Exclusion of frail older adults from clinical trials
- Comprehensive geriatric assessment

Transitions in Frailty Status

- Example

Considerations and Implications for Assessment of Frailty Status in older adults?

Is Frailty More than a Phenotype/Aggregate of Measures Indicating Vulnerability?

- If answer is “Yes” – Etiology
- Unique condition
- Distinct from disability or any other
- Variables need to be selected among those hypothesized to be in a causal pathway
- Correlation among variables given common underlying mechanism
- Research to identify pathophysiologic basis, and specific treatment for frailty in the hope that this will translate into lower disability risk
- Frailty is a cause, not merely a marker of risk

Considerations and Implications for Assessment of Frailty Status in older adults?

Is Frailty More than a Phenotype/Aggregate of Measures Indicating Vulnerability?

No

Main Goal: Risk Prediction

All possible variables that maximize risk prediction

Variables do not need to be thought of as “causal”

Variables do not need to be biologically correlated among themselves

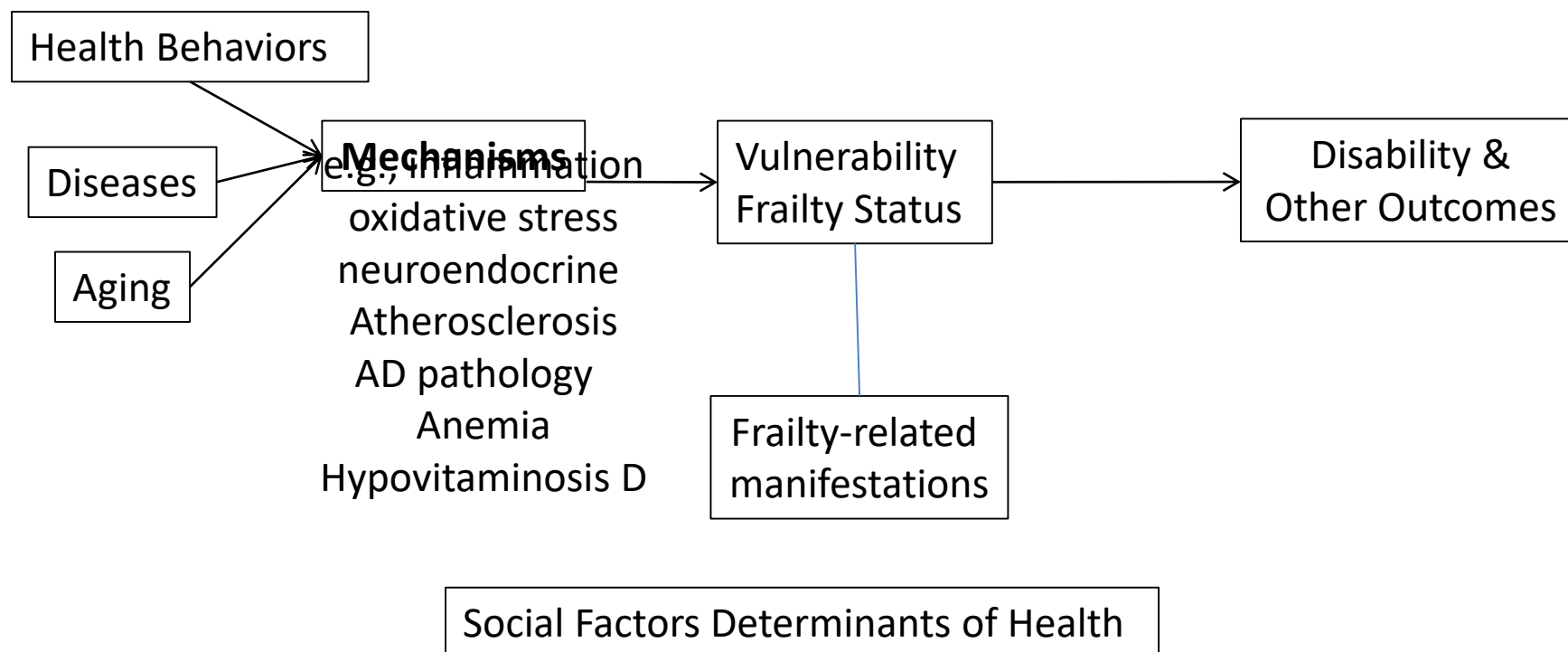
Don't even need to be Medical

Do not need to attempt to distinguish between “frailty”, disability, falls, multimorbidity, fall

Context Example: Risk stratification in healthcare systems for planning, healthcare delivery effici

Is Frailty More than an Aggregate of Measures Indicating Vulnerability?

- Biological perspective
 - Common underlying pathophysiologic basis of which physical and cognitive decline are clinical manifestations?



Is Frailty More than a Phenotype/Aggregate of Measures Indicating Vulnerability?

Frailty: Increased Vulnerability

Increased Risk of Adverse Outcomes

Main Goal: Risk Prediction

Frailty in Older Adults

- Dominant theme in Geriatrics
- Prevention and treatment of frailty in older adults has been recognized as a cornerstone of geriatric medicine
- Health status heterogeneity not explained by age, diseases, or even traditional measures of disability
- Function, quality of life
- Compression of morbidity in aging societies
- Increasing attention in other disciplines

Frailty in Older Adults

- Context/timeline (my own – individualize presnettaion)
- Katz ADL
- Falls –
- Fiatarone
- SPPB
- Linda's seminar
- Fried paper
- OAIC Pepper Center

Frailty in Older Adults

- Enhanced vulnerability
 - Increased risk of major adverse outcomes
 - Disability
 - Healthcare utilization
 - ER visits, recurrent hospitalization, NH admission
 - Mortality
- Resilience Spectrum



Frailty in Older Adults

- Not the same as aging
 - Frailty \neq aging,
 - Frailty \neq “normal” age-related functional decline
 - Frailty as a state of accelerated aging, decline
- Thus, potentially preventable

Frailty in Older Adults

- **Dominant theme in Geriatrics**
 - Compression of morbidity in aging societies
- **Enhanced vulnerability**
 - Adverse Outcomes
 - Disability
 - Healthcare utilization
 - ER visits, recurrent hospitalization, LoS, NH admission
 - Mortality
 - Health status heterogeneity not explained by chronologic age or diseases

Frailty in Older Adults

- Context/timeline (my own – individualize presnettaion)
- Katz ADL
- Falls –
- Fiatarone
- SPPB
- Linda's seminar
- Fried paper
- OAIC Pepper Center

Frailty in Older Adults

- Dominant theme in Geriatrics
- Compression of morbidity in aging societies
 - Efforts above and beyond traditional diseases
 - Selected efforts
 - 1992: Buchner & Wagner. Preventing frail health (Clin Geriatr Med)
 - 1993:
 - 1994 - Tinetti et al. Multifactorial intervention for falls
 - 1994 - Fiatarone et al. Exercise for very elderly in LTC
 - 1995 – Guralnik et al. SPPB
 - 2001 – Fried et al. Frailty phenotype

Tinetti et al. N Engl J Med 1994;351:1179-86

Fiatarone et al. N Engl J Med 1994;351:1179-86

Guralnik et al. N Engl J Med 1995;353:954-61

Frailty in Older Adults

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Psychosocial Factors and Frailty

- **Individual**

- Lower education
- Financial strain
- Lower positive affect
- Loneliness
- Lower levels of social support
 - Progression of frailty
- Life space restriction

- **Neighborhood**

- Less ethnically dense neighborhood
- Deprived SES neighborhood

Frailty Research Agenda

- Test frailty interventions
- Limited knowledge, clinical trial data
 - Frailty prevention and/or reversal, and disability prevention and/or postponement
- Mostly indirect
 - Frailty components (e.g., strength) as targets and frailty outcomes (e.g., mobility disability)
- Most robust evidence to reduce vulnerability
 - Exercise; i.e., strength and aerobic

Frailty Research Agenda

- Sarcopenia is central to frailty
 - Key clinical manifestation
 - Shared mechanisms
 - Key intervention target for frailty prevention
- Assuming sarcopenia, frailty, and disability have independent added values in primary care setting
 - Epidemiologic research to explore integration of assessment for frailty, sarcopenia, and disability

Frailty Research Agenda

- Comprehensive Geriatric Assessment
- Sarcopenia is central to frailty
- Loss of muscle mass
 - Decrease in Type I muscle fibers; muscle atrophy
- Decrease in strength/decade:
 - 60-79: 15%
 - >80: 30%
- Results in decreased power, walking speed

Evans; Fiatarone; Roberts; DeLateur; Buchner

Conclusion

- Comprehensive geriatrics management approaches
- Burdened in the past
- CGA in the 90's
- Falls more recently
- Need to identify those who may benefit from comprehensive geriatric assessment
- What is the best approach – core components –
- What should the desired outcomes be?