Frailty Ascertainment:
Beginning of the pathway to treatment

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Introduction
Whither "frailty ascertainment"?

- "Geronmetrics"
  - a.k.a.: econometrics, psychometrics, biometrics
  - Goal: Accurate and precise measurement of complex health states or spectra
- Rigorous measurement is essential to
  - Sensitivity, specificity for genetic, other discovery
  - Theory operationalization, testing
  - Correctly targeted, evaluated interventions
- Worth measuring as stand-alone construct?
  - If not, pursuing items under the last bullet makes little sense

Introduction
Geronmetric Measurement

- Proposition: Most effective when attacked "from both ends"
  - Mechanisms / basic science
  - Phenotype / validity
    - Face : Sensible?
    - Content : Captures all aspects?
      Excludes extraneous aspects?
    - Criterion : Predicts relevant outcomes?
    - Construct : Captures assessment target?

This module aims to…

- Present theory identifying frailty
- Propose a frailty validation methodology
- Present measurement validation results
- Highlight areas of promise for future work

Theory: Frailty
Prevailing perspectives

- Obsolete: frailty = disability; disease
- Rockwood et al: accumulation of deficits; proximity to death
- Lipsitz: Loss of dynamical complexity
- Studenski: Geriatrician consensus
- Deeg: Static versus dynamic frailty—aggregate markers vs. changes

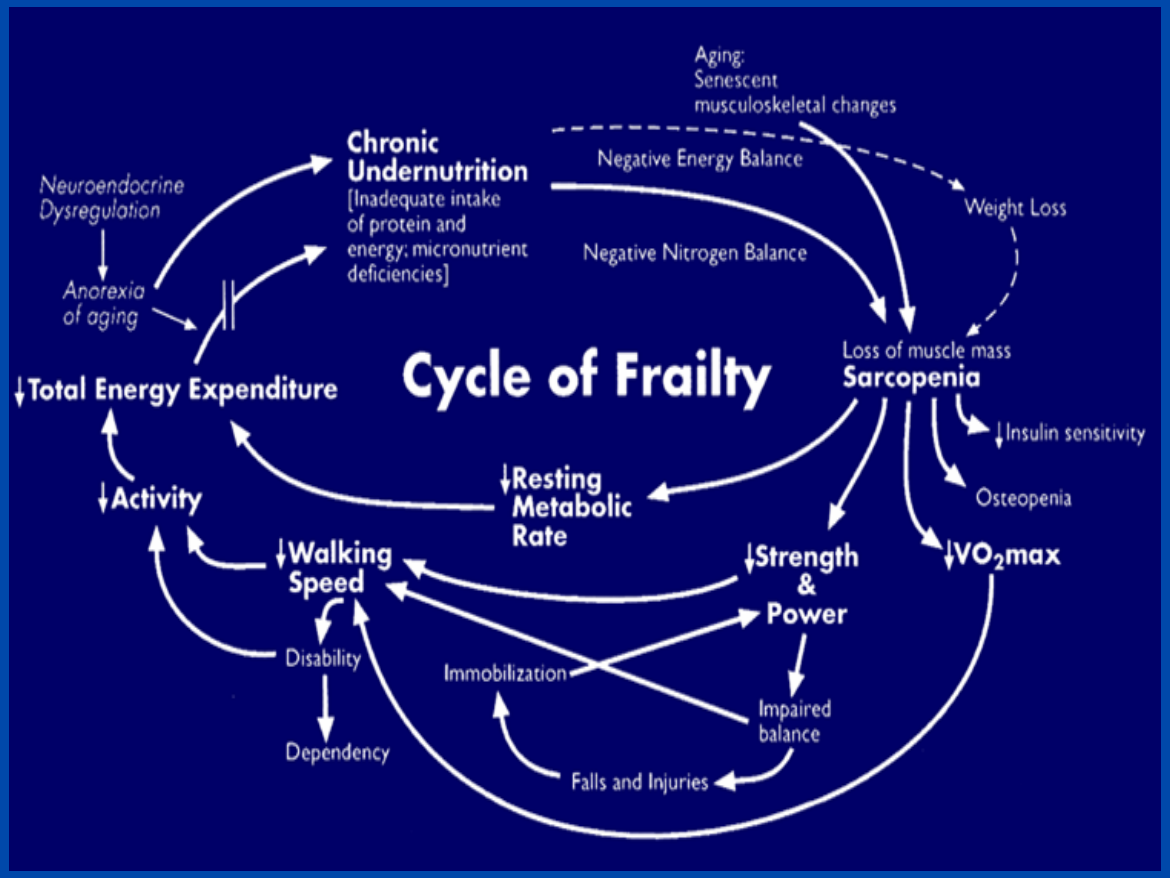
References 6; 24-26

Theory: Frailty…

- Is recognizable to (some?) geriatricians
- Has adverse geriatric consequences
- An outcome of dysregulation in multiple physiological systems
  - Inflammatory? Hormonal? Nutritional? Etc.?
- Is a syndrome of decreased resiliency and reserves manifesting in multiple domains
  - e.g., see next slide
- Is distinct from disease or disability

References 1-17

The Syndromic Cycle Theory



3-Fried et al., J Gerontol 56:M146-56; Bandeen-Roche et al., J Gerontol, 2006

Frailty Measurement Validation Methodology

- Criterion validity: "Frailty" = combination of aspects which well predicts adverse outcomes, or is well predicted by hypothesized risk factors

- Methods: Standard regression models (here); also neural nets, regression trees, logic regression, etc.

Frailty Measurement Validation Methodology

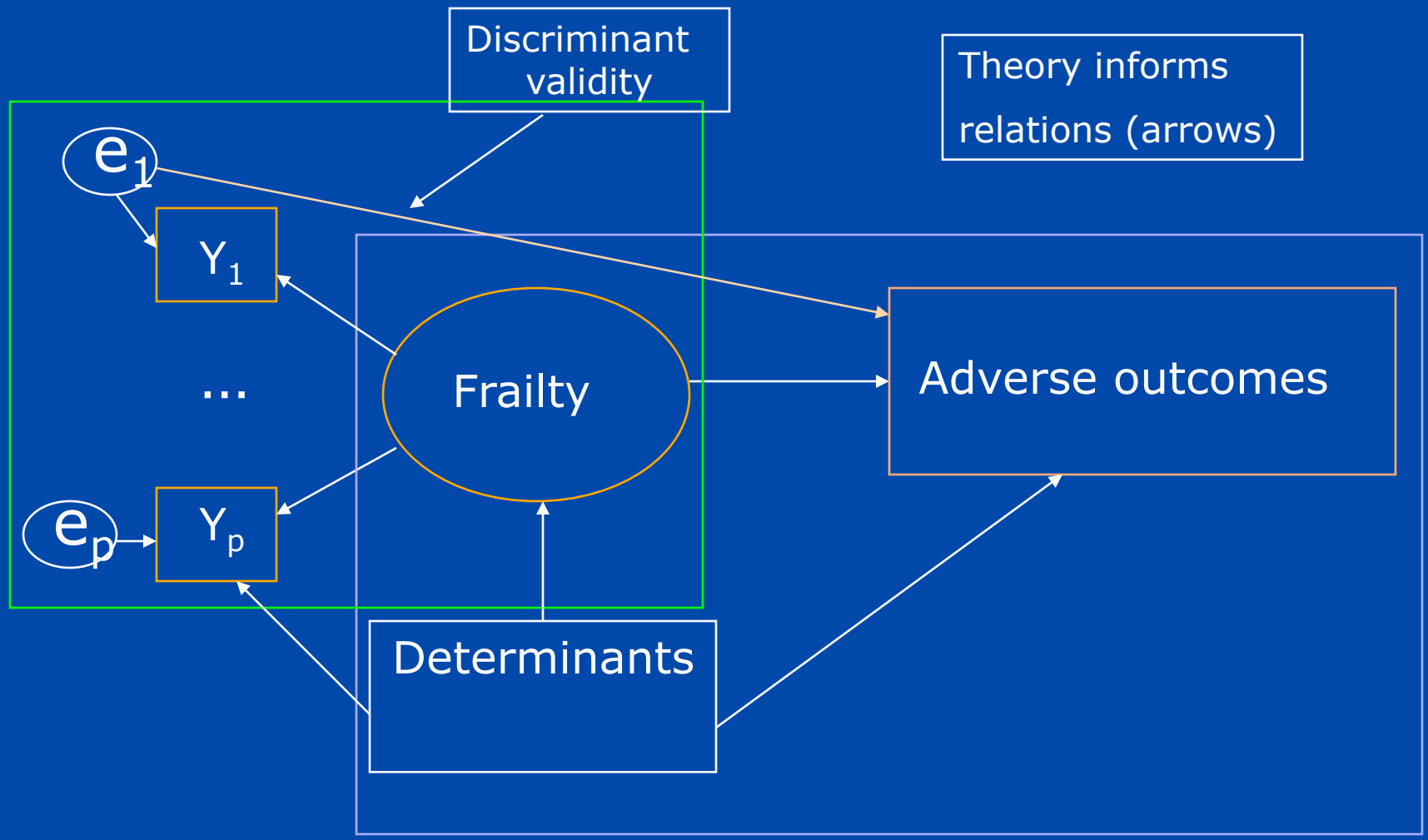
- Content validity: Science — Clarity in construct definition
  - Arguably: Key source of current debate
- Construct validity: Theory testing
  - Proposal: Latent ("underlying") variable modeling — panels to follow
- Not a focus of this module, but worth keeping in mind: reliability of measures

Frailty Construct Validation
Latent Variable Methodology

- Views frailty as underlying; inferred through surrogates

- Then interest is in
  - Measurement: How does underlying frailty relate to measured criteria?
  - Structure: Relation of frailty to putative etiology or consequences

Frailty Construct Validation
Latent Variable Methodology



Syndrome Validation
Methods

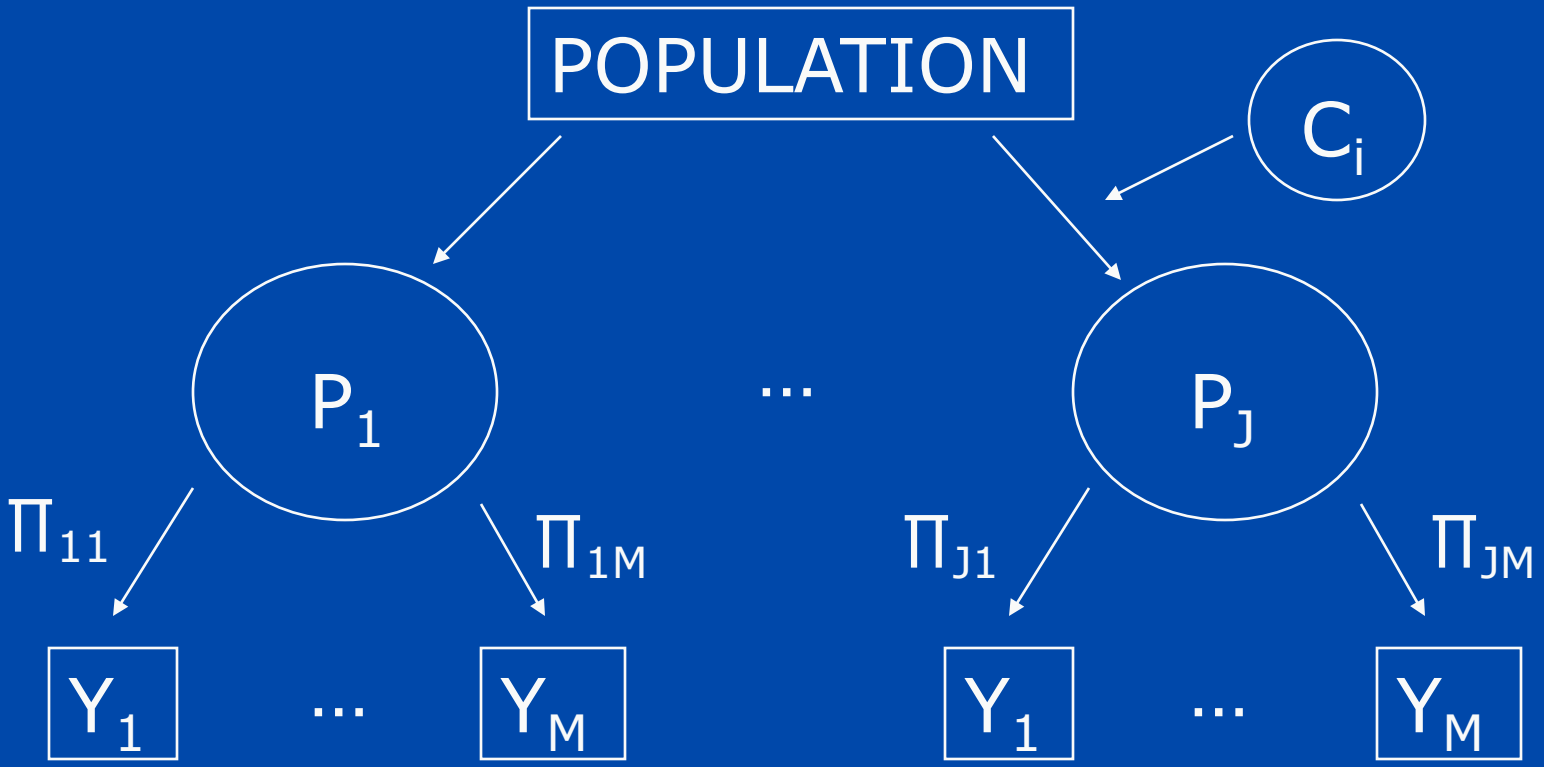
- Internal convergent validity

- Criteria manifestation is syndromic

  "*a group of signs and symptoms that occur together and characterize a particular abnormality*"[18]

  - Method: Latent class analysis[19,27]

Syndrome validation
Method: Latent class analysis



19-Goodman, 1974; 27-McCutcheon, 1987

Syndrome validation
Method: Latent class analysis

- Seeks clinically homogeneous subgroups
- Features that characterize latent groups
  - Prevalence in overall population
  - Percentage manifesting each criterion
- If criteria characterize syndrome:
  - At least two groups (otherwise, no co-occurrence)
  - No subgrouping of symptoms (otherwise, more than one abnormality characterized)

Frailty Construct Validation
Method Philosophy

- Role of latent variable modeling?
  - ~~Reveal underlying truth?~~
  - Operationalize and test theory
    - Convergent and discriminant
  - Sensitivity analyses
    - Do minor changes to theory greatly affect conclusions?

Methods

Data: Women's Health & Aging Studies[20-21]

- Fried et al. (2001)[3] measures: 5 criteria
  - Robust = none; Intermediate=1-2; Frail=3 or more

Frailty-defining criteria: WHAS

Criterion	Definition	%
1. **Weight loss**	Either of: i) Weight at age 60–weight at exam >= 10% of age 60 weight.; ii) BMI at exam < 18.5.	12.7
2. **Exhaustion**	Self report of any of: i) low usual energy level (<=3, range 0-10); felt unusually (ii) tired (iii) weak in last month	14.1
3. **Low Energy Expenditure**	90 on activity scale (6 items)	19.8
4. **Slowness**	walking 4m: speed <= 4.57/7 for height <= 159 cm; speed <= 4.57/6 for height > 159 cm	31.3
5. **Weakness**	Grip strength: <= 17 for BMI <= 23; <=17.3 for BMI 23.1 - 26 <= 18 for BMI 26.1 – 29; <= 21 for BMI > 29As for CHS.	20.8
OVERALL FRAILTY STATUS	Robust	44.9
	Intermediate	43.8
	Frail	11.3

Results
Face Validity

- Face validity
  - Criteria reflect geriatric impression
  - WHAS I: prevalence increases with age
  - WHAS: prevalence higher among more disabled (25.4%) than overall (11.3%)
- Cross validity
  - Prevalence similar across cohorts (11.3% in WHAS; 11.6% in age-matched CHS women)

Results
Criterion Validity

Association of Baseline Frailty Status and Risk of Incident Adverse Events, Combined WHAS I (rounds 1, 4, 7) and WHAS II (rounds 1, 2, 3) Cohorts (n=784)

Outcome	Adjusted Hazard Ratios (95% Confidence Intervals)	
	Intermediate	**Frail**
Fall (n=560)	0.92 (0.63, 1.34)	1.18 (0.63, 2.19)
Severe ADL Disability (n=612)	5.68 (2.41, 13.42)	15.79 (5.83, 42.78)
Severe IADL Disability (n=698)	3.53 (1.20, 10.35)	10.44 (3.51, 31.00)
Hospitalization (n=715)	0.99 (0.67, 1.47)	0.67 (0.33, 1.35)
Permanent Nursing Home Entry (n=750)	5.16 (0.81, 32.79)	23.98 (4.45, 129.2)
Death (n=766)	3.50 (1.91, 6.39)	6.03 (3.00, 12.08)

- Phenotype strongly predicts adverse outcomes
- Phenotype predicted by signs of systemic dysregulation: inflammatory, immunological, hormonal, nutritional

Conditional Probabilities of Meeting Criteria in Latent Frailty Classes WHAS

Criterion	2-Class Model		3-Class Model		
	CL. 1 NON-FRAIL	CL. 2 FRAIL	CL. 1 ROBUST	CL. 2 INTERMED.	CL. 3 FRAIL
Weight Loss	.073	.26	.072	.11	.54
Weakness	.088	.51	.029	.26	.77
Slowness	.15	.70	.004	.45	.85
Low Physical Activity	.078	.51	.000	.28	.70
Exhaustion	.061	.34	.027	.16	.56
Class Prevalence (%)	73.3	26.7	39.2	53.6	7.2

Bandeen-Roche et al., 2006

Results
Syndrome Validation

- Two class model fit is good
  - Pearson χ^2 p-value=.22; minimized Akaike[22] & Bayesian[23] Information Criteria
- In three-class model: mean # of criteria in "intermediate," "frail" groups = 1.26, 3.42—in line with defined cutoffs
- Frailty criteria prevalence stepwise across classes—no subclustering
- Syndromic manifestation well indicated

Measurement of Frailty
Discussion: Areas of Promise

- Content validity: All aspects covered?
  - Cognitive decline?
  - Depression / anxiety?
  - Physiotype rather than phenotype?

- Construct validity
  - External validity
    - Link to multisystemic dysregulation
    - Specificity re vulnerability to stressors
  - Discriminant: What is frailty not?

Discriminant Validity
More than Component Parts

- WHAS: Disease-adjusted analysis, mobility disability vs. components
  - Slowness=strongest predictor

    OR=17, 95% CI [7.8, 38] vs.

    6.6, 95% CI [2.2, 20] for weakness
  - All but weight loss predict (multiply)

Discriminant Validity Data
More than disease, disability (WHAS)

- Frail, # diseases associated, not redundant
  - "Frail" rare if no (2%) or 1 (5%) disease
  - "Intermediate" not rare these cases (>29%)
  - Many with comorbid diseases robust (>28%)

- Frailty strongly predicts mobility disability, independently of age, # diseases
  - OR for severe disability = 29 (95% CI [9.3,88])
  - Little interaction w disease: not severity marker

Discriminant Validity Data
More than disease (WHAS)

- Mortality analysis with propensity scoring

ADJUSTMENT	FRAILTY OR (CI)
None	2.42 (1.81,3.24)
Disease count, age	1.81 (1.33,2.45)
Cluster-based C/D/S vars.	1.74 (1.28,2.36)
Elements of score	1.69 (1.23,2.30)
Propensity score	1.67 (1.22,2.28)
P. Score: Mid-90	1.51 (1.07,2.13)

Frailty Ascertainment
Discussion: Areas of Promise

- Criterion validity
  - …i.e. utility for screening, diagnosing & targeting adverse geriatric outcomes
  - Needed
    - Delineation of predictive accuracy
    - Reliability delineation and refinement
    - Comparison among competitors
    - Threshold relationships?

Frailty Ascertainment: Summary

- Rigorous frailty ascertainment is essential to treatment development!
- A key element of rigor: validity
  - Does ascertainment "hit the target"?
  - Target: involves theory
- Working theory:

  Frailty is a free-standing syndrome of decreased resiliency and reserves that results from dysregulation in multiple physiological systems and has adverse geriatric consequences

- Evidence presented re Fried et al. (2001) phenotype:

  Face, criterion, and construct validity for syndrome with adverse consequences

Acknowledgments

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  Johns Hopkins Older Americans Independence Center, National Institute on Aging, Brookdale National Foundation

- References: See attached

- Basis:

  PHENOTYPE OF FRAILTY: CHARACTERIZATION IN THE WOMEN'S HEALTH AND AGING STUDIES

  J Gerontol Med Sci, 2006