Frailty and Depression in Late Life

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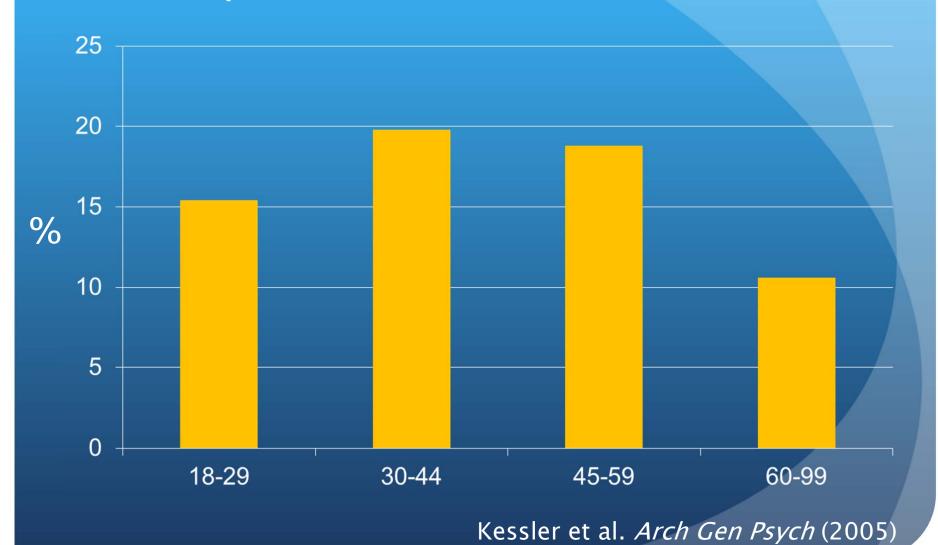New York State Psychiatric Institute

Disclosures

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Major Depressive Disorder

- Depressed Mood OR Loss of interest or pleasure
- And four of the following:
  - Significant weight loss/gain (+ 5% of body weight in a month)
  - Insomnia or hypersomnia
  - Psychomotor agitation/retardation
  - Fatigue or loss of energy
  - Feeling worthless or guilty
  - Difficulty concentrating
  - Recurrent thoughts of death

- Clinically significant functional impairment

Lifetime prevalence of MDD: NCS-R

Kessler et al. *Arch Gen Psych* (2005)

Depression in late life

- 3-7% of adults over the age of 65 have a dx of MDD
    - 15% have significant but subthreshold symptoms
    - One of the leading causes of disability and functional impairment in the world
    - Highest rate of successful suicide attempts
        - Older white men (strong correlation with recent visits to doctor)
    - Under recognized and hence under treated
        - DSM system not created with late life in mind
            - Geriatric Depression Scale
                - Created to remove somatic items (concentration issues, fatigue, sleep deficits) that may have multiple etiologies and not be due to depression per se

Causal attributions of symptoms by age: Appetite loss

Age 18 – 39
Total symptom endorsement: 22.4%

Age 40 – 59
Total symptom endorsement: 24.6%

Age 60+
Total symptom endorsement: 19.3%

■ Psychiatric

■ Illness/injury or drugs/alcohol/medication

Mezuk & Eaton *Handbook of Measurement* (2010)

Causal attributions of symptoms by age: Fatigue

Age 18 – 39
Total symptom endorsement:
11.8%

Age 40 – 59
Total symptom endorsement:
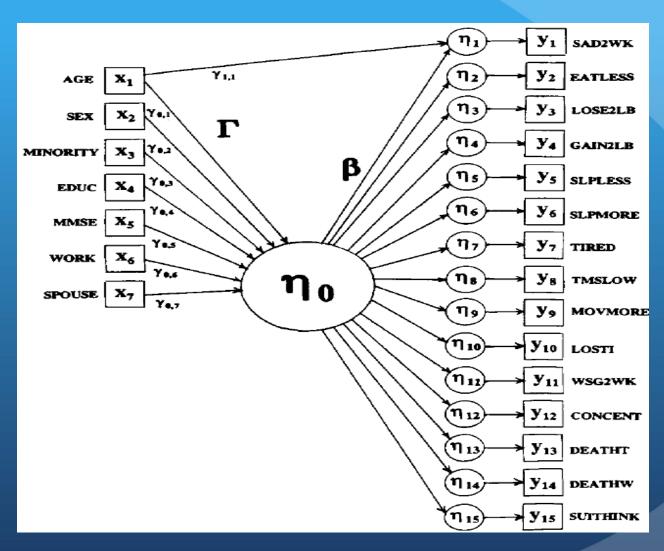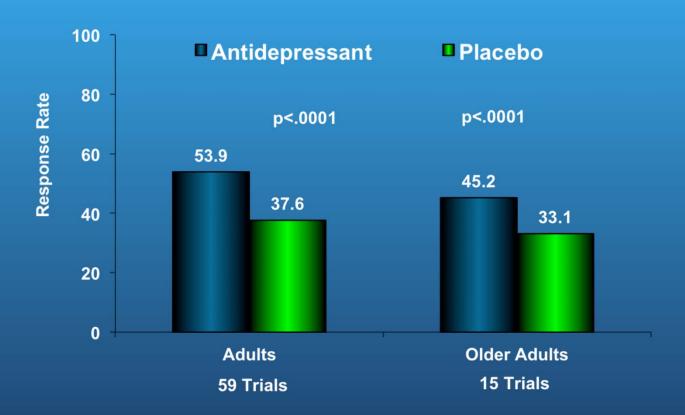10.3%

Age 60+
Total symptom endorsement:
10.2%

■ Psychiatric

■ Illness/injury or drugs/alcohol/medication

Mezuk & Eaton *Handbook of Measurement* (2010)

Depression without sadness?

From Gallo, Anthony & Muten (1994)

Comparison of response rates in placebo controlled trials of antidepressant medications

Tedeschini et al. J Clin Psychiatry 2011

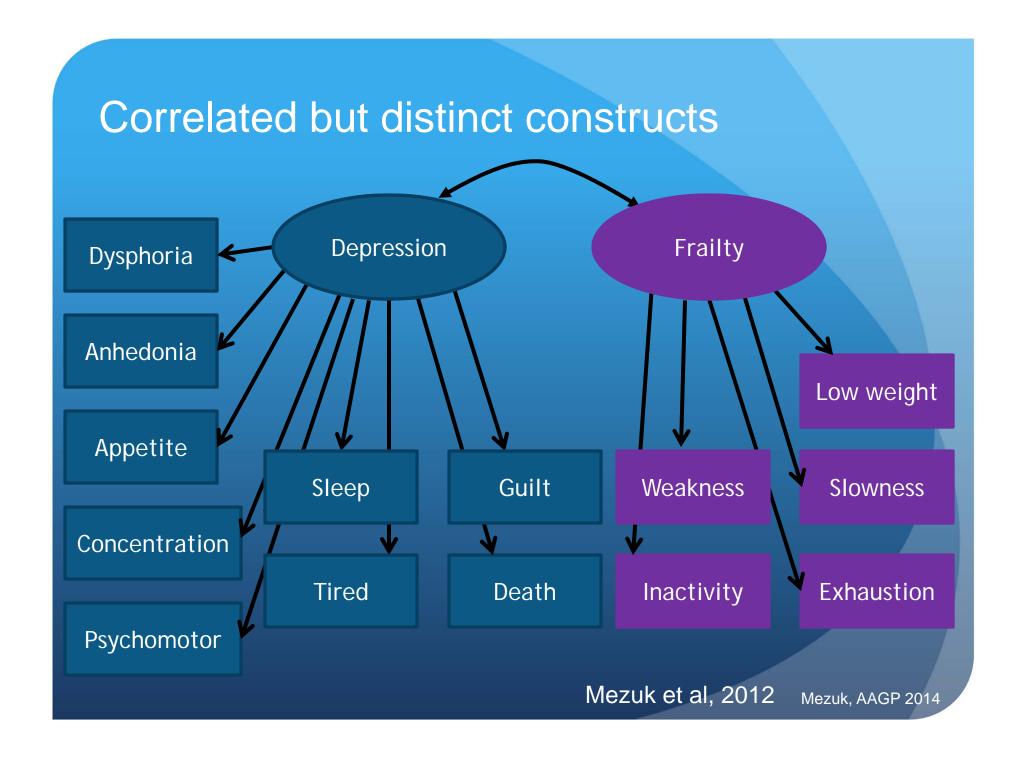# Identifying characteristics in late life depression

- May identify different etiologies, resulting in different treatment strategies targeting different mechanisms
  - For example:
    - Executive dysfunction
      - Tests: Trail-making Test A/B, Stroop, Matrix Reasoning, Digit Symbol
      - Marks what is called a vascular depression
        - Associated with vascular diseases/risk factors including HTN, DM, smoking, obesity
        - Increased white matter hyperintensity burden
        - Attenuated response to antidepressant medications

Frailty and depression in late life

- <u>Physical System</u>: Somatic characteristics of depression phenomenologically similar to frailty
  - Psychomotor slowing – slow gait
  - Low energy – fatigue
  - Decreased physical activity – Decreased physical activity
  - Weight loss – weight loss
- Are frailty and depression separate constructs or merely different manifestations of the same underlying syndrome?

Why is frailty important in the context of late life depression?

- 10 years ago, Ira Katz introduced the concept of frailty in geriatric psychiatry. He concluded:

  - "The parallels between depression and frailty are readily apparent. Depending on the definitions used, it is possible to make a case for each of these conditions as a cause, consequence, or comorbidity of the other. It is also possible to argue for their congruence; within limits, they may be different labels for the same syndrome. However, certain conclusions are not merely semantic. Multidisciplinary research on depression and frailty will be necessary to advance knowledge of mechanisms and interventions for both."

- Inflammation as common underlying mechanism?

Correlated but distinct constructs

Depression — Dysphoria, Anhedonia, Appetite, Concentration, Psychomotor, Sleep → Tired, Guilt → Death

Frailty — Low weight, Weakness → Inactivity, Slowness, Exhaustion

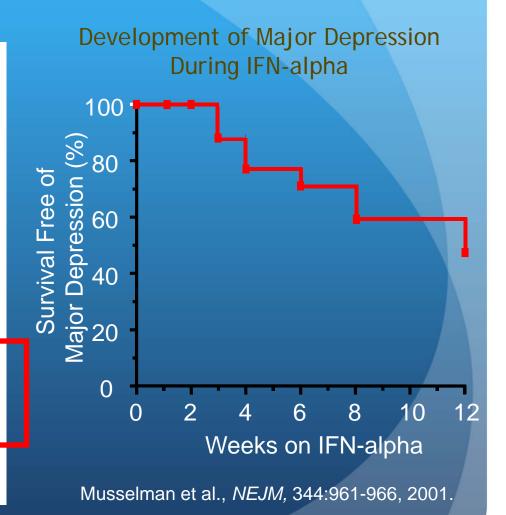Mezuk et al, 2012   Mezuk, AAGP 2014

Overlapping constructs

- Among those classified as not depressed (77% of respondents)
  - 5.9% were classified as frail

- Among those classified as moderately depressed (20% of respondents)
  - 69.0% were classified as frail

- Among those classified as severely depressed (3% of respondents)
  - 100% were classified as frail

Behavioral Changes During the First 12 weeks of High Dose IFN-alpha for Malignant Melanoma

	Percent
Depressive Symptoms	
Depressed mood	60
Anhedonia	30
Suicidal Thoughts	10
Feelings of Guilt	5
Anxious Symptoms	
Tension/Irritability	50
Anxious Mood	45
Fear	15
Cognitive Symptoms	
Loss of Concentration	30
Memory Disturbances	15
Word-finding Problems	15
Episodes of Confusion	10
Indecisiveness	10
Neurovegetative Symptoms	
Fatigue/ Loss of Energy	80
Abnormal Sleep	45
Psychomotor Retardation	40
Abnormal Appetite	35
Somatic Symptoms	
Pain	55
Gastrointestinal Symptoms	50

Development of Major Depression During IFN-alpha

Musselman et al., *NEJM,* 344:961-966, 2001.

Capuron et al., *Neuropsychopharmacology*, 26:643-652, 2002.

Felger, AAGP 2014

The Depressed-Frail Phenotype: High Risk Clinical Population

Clinical trajectory of the depressed-frail phenotype

- To identify salient characteristics of frailty that increase risk of death in depressed elders.
  - Nordic Research on Ageing Study (NORA)
    - 1027 75 year old men (n=436) and women (n= 591)
      - Mortality data extending out 12 years

- Depression (3 categories via CES-D)
  - More women, slowed processing speed, greater executive dysfunction, greater IADL impairment
  - Frailty
    - Slower Gait speed via 10-m walk (m/s)
    - Greater weakness via handgrip strength (kgf)
    - Greater levels of fatigue via Avlund Mob-T Scale
    - Lower physical activity levels via self-report

Brown et al., 2014

Depression and frailty
Combined models of frailty characteristics

Frailty	No Depression (n = 543) Hazard ratio (95% CI)		Depression (n = 261) Hazard ratio (95% CI)	
	Men (n=278)	Women (n=265)	Men (n=84)	Women (n=177)
Low Activities Yes vs. No	1.76 (1.17, 2.65)[a]	1.34 (0.78, 2.28)	1.68 (0.76, 3.74)	1.56 (0.93, 2.61)
Exhaustion Yes vs. No	1.51 (1.00, 2.28)	1.54 (0.92, 2.56)	1.48 (0.69, 3.15)	1.94 (1.11, 3.40)[a]
Slow Gait Speed Yes vs. No	1.54 (1.05, 2.26)[a]	1.30 (0.79, 2.14)	1.52 (0.67, 3.45)	1.84 (1.05, 3.21)[a]
Low Grip Strength Yes vs. No	1.02 (0.65, 1.59)	1.83 (1.06, 3.18)[a]	1.35 (0.64, 2.81)	1.19 (0.70, 2.02)

Cox regression models stratified by site and gender with one frailty characteristic entered into each model; results did not differ with comorbidities added
[a] $P < .05$; [b] $P < .01$; [c] $P < .001$

Brown et al., 2014

Gait Speed x Gender x Depression

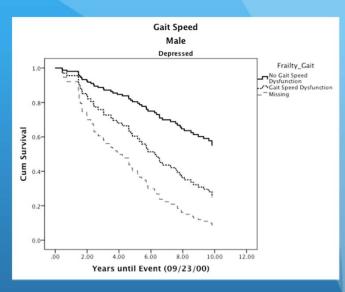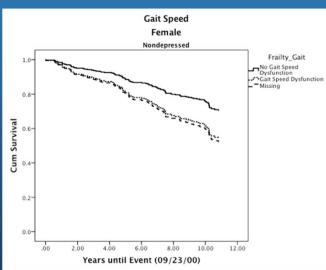

Mortality rates

Nondepressed Men:
No gait: 48%
Gait: 75%

Depressed Men:
No gait: 45%
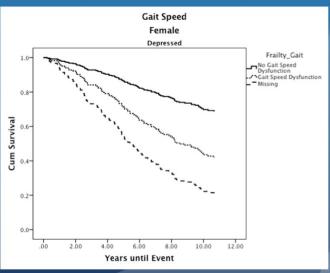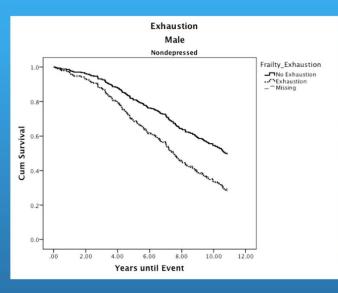Gait: 71%

Nondepressed Women:
No gait: 26%
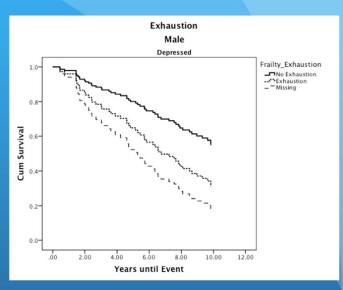Gait: 40%
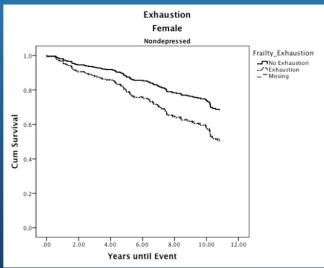
Depressed Women:
No gait: 32%
Gait: 58%

Brown et al., 2014

Exhaustion x Gender x Depression

Mortality rates
Nondepressed Men:
No exhaust: 48%
Exhaust: 70%
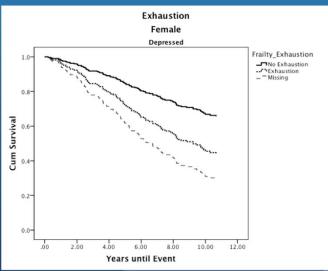
Depressed Men:
No exhaust: 45%
Exhaust: 59%

Nondepressed Women:
No exhaust: 30%
Exhaust: 47%

Depressed Women:
No exhaust: 33%
Exhaust: 63%

Brown et al., 2014

Depressed-frail phenotype

- Questions:
  1. How does the presence of frailty characteristics impact mortality in older adults with depression?
     - Depression enhanced the effect of slowed gait and exhaustion on mortality
     - But only in women?
  2. Are there common physiological mechanisms that mark a particular manifestation of the phenotype?
     - Inflammation?

Health ABC:
Inflammation, Gait, Depression, and Mortality

A longitudinal study of 3075 well-functioning African American and Caucasian adults aged 68-80 at the time of initial eval

The aims of this study were to:
1. Identify the trajectories of inflammation, depression, and slow gait and determine their association
2. Determine the order in which the conditions manifest
3. Investigate the individual and joint associations between mortality and trajectories for these conditions
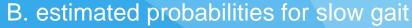
Variables:
- Depression: CES-D $\geq$ 10
- Slow Gait: < 1.02 m/s
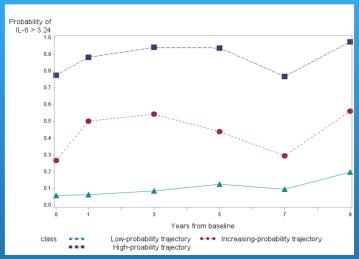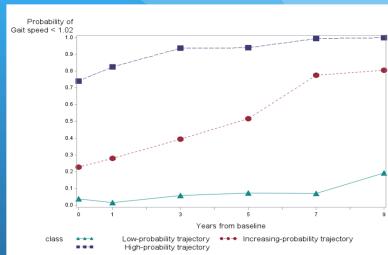- Inflammation: Interleukin 6 > 3.24 pg/mL

Analytic Tools:
- Multivariate Longitudinal Latent Class Growth Analysis
  - Uses all of the longitudinal data, models missing, thus less reliance on single point prevalence analyses (baseline values)

Brown et al., in prep

Health ABC: Latent Class Analysis

A. estimated probabilities for inflammation

B. estimated probabilities for slow gait

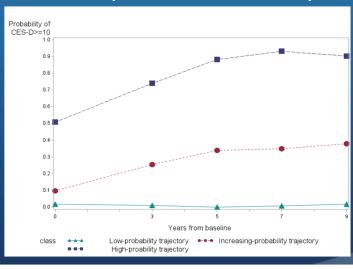## C. estimated probabilities for depression

Trajectories of inflammation associated with:
- slow gait r =.40, P<.001
- depression r =.11, P<.001
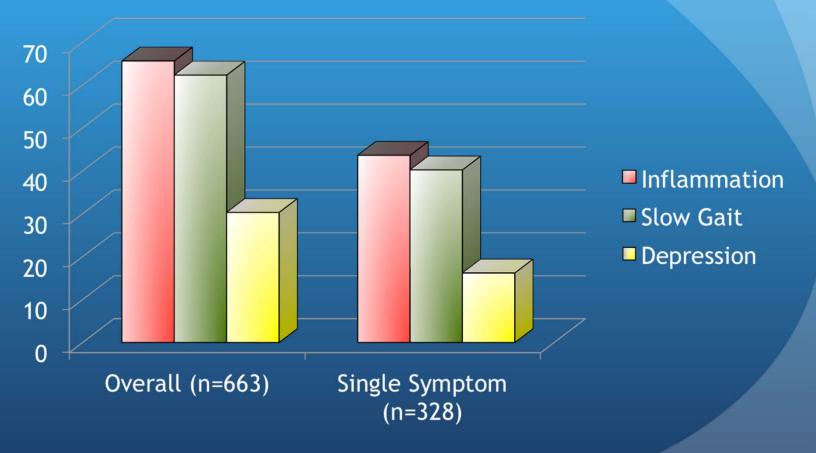
Trajectories of slow gait with:
- depression r = .49, P<.001

Trajectories of inflammation associated with:
- higher BMI, more vascular and cardiovascular diseases
- Slower gait, lower energy
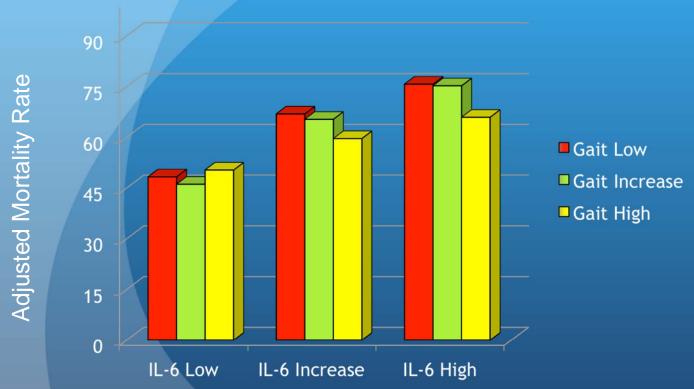
Brown et al., in prep

HABC: Order of presentation

Incidence rates were examined to identify the order of presentation over 10-years in elders with increasing- or always-high-probability trajectories of inflammation, depression, and slow gait

Brown et al., in prep

HABC: Covariate Adjusted Mortality Rates

Main effect of trajectories of inflammation; two-way interaction between trajectories of slow gait and depression

Covariates adjusted for include baseline age, sex, body mass index, 3MS, baseline medical comorbidity (vascular disease, physical impairment, respiratory illness, cardiovascular disease, cerebrovascular disease, and malignant cancer), and baseline anti-inflammatory medication use.

Brown et al., in prep

HABC: Covariate Adjusted Mortality Rates

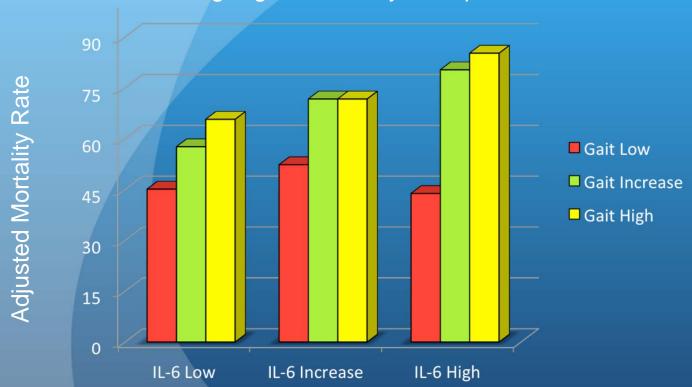Increasing/High-Probability of Depression

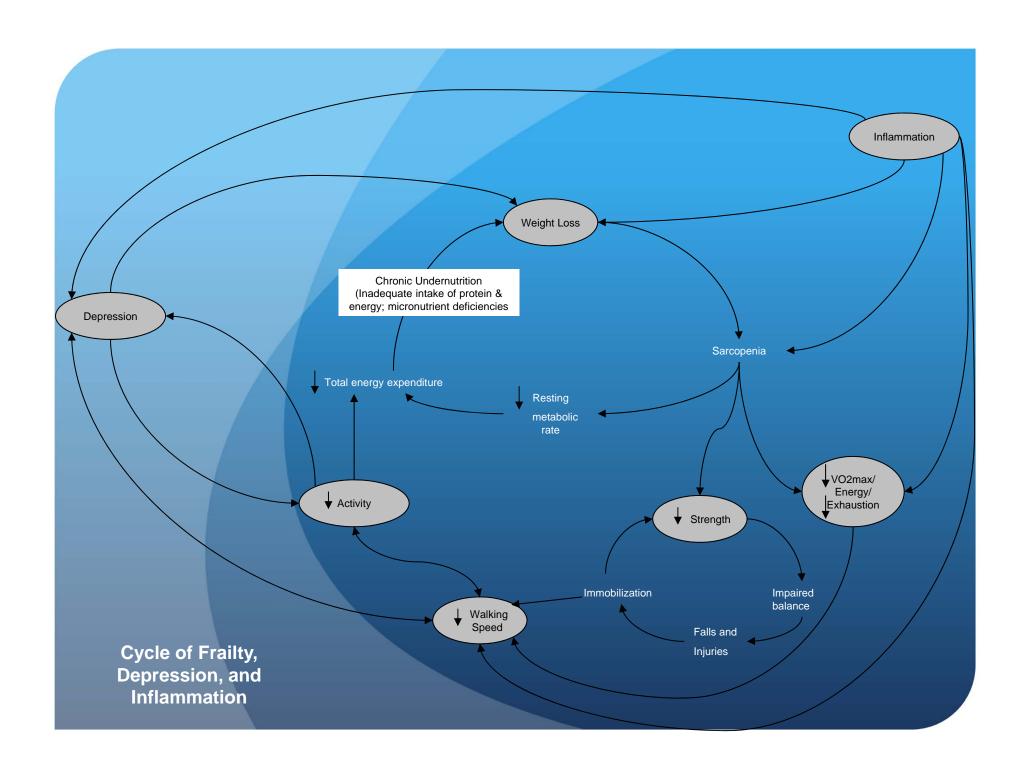Main effect of trajectories of inflammation; two-way interaction between trajectories of slow gait and depression

Covariates adjusted for include baseline age, sex, body mass index, 3MS, baseline medical comorbidity (vascular disease, physical impairment, respiratory illness, cardiovascular disease, cerebrovascular disease, and malignant cancer), and baseline anti-inflammatory medication use.

Brown et al., in prep

Conclusions:
Health ABC Study

- Inflammation, depression, and slow gait define a phenotype at grave risk of death
  - Trajectories of Inflammation has an independent effect on mortality after accounting for covariates
  - The effect of trajectories of slow gait on mortality depends on depression trajectory status

- Multiple pathways into phenotypic cycle
  - Most common are via inflammatory or mobility pathways
  - Depression appears to be a secondary process in late life

Cycle of Frailty, Depression, and Inflammation

Inflammation

Weight Loss

Chronic Undernutrition
(Inadequate intake of protein &
energy; micronutrient deficiencies

Depression

Sarcopenia

↓ Total energy expenditure

↓ Resting metabolic rate

↓ Activity

↓VO2max/ Energy/ Exhaustion

↓ Strength

Immobilization

Impaired balance

↓ Walking Speed

Falls and Injuries

Implications and Future Directions

- Do specific frailty characteristics predict response to antidepressant treatment in older depressed patients?
  - If so, what is the underlying mechanism that identifies them?
    - Inflammation?
      - Slow gait: Dopamine fx in basal ganglia
        - Anhedonia, amotivation
      - Differentiate "I don't feel like doing anything" and "I don't have the energy to do anything"
        - Fatigue and its biological underpinnings
    - Differences may identify specific mechanisms to target via different intervention implementation
      - Exercise, anti-inflammatories, antidepressant medications, nutrition, problem solving and/or cognitive behavioral therapy

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