

The Aging Immune System and the Physiology of the Inflammatory Response

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The Clinical Questions

- Why do older people get sick all the time?
- Why do diseases cluster together late in life?
- Is there something biological that makes some people more vulnerable?

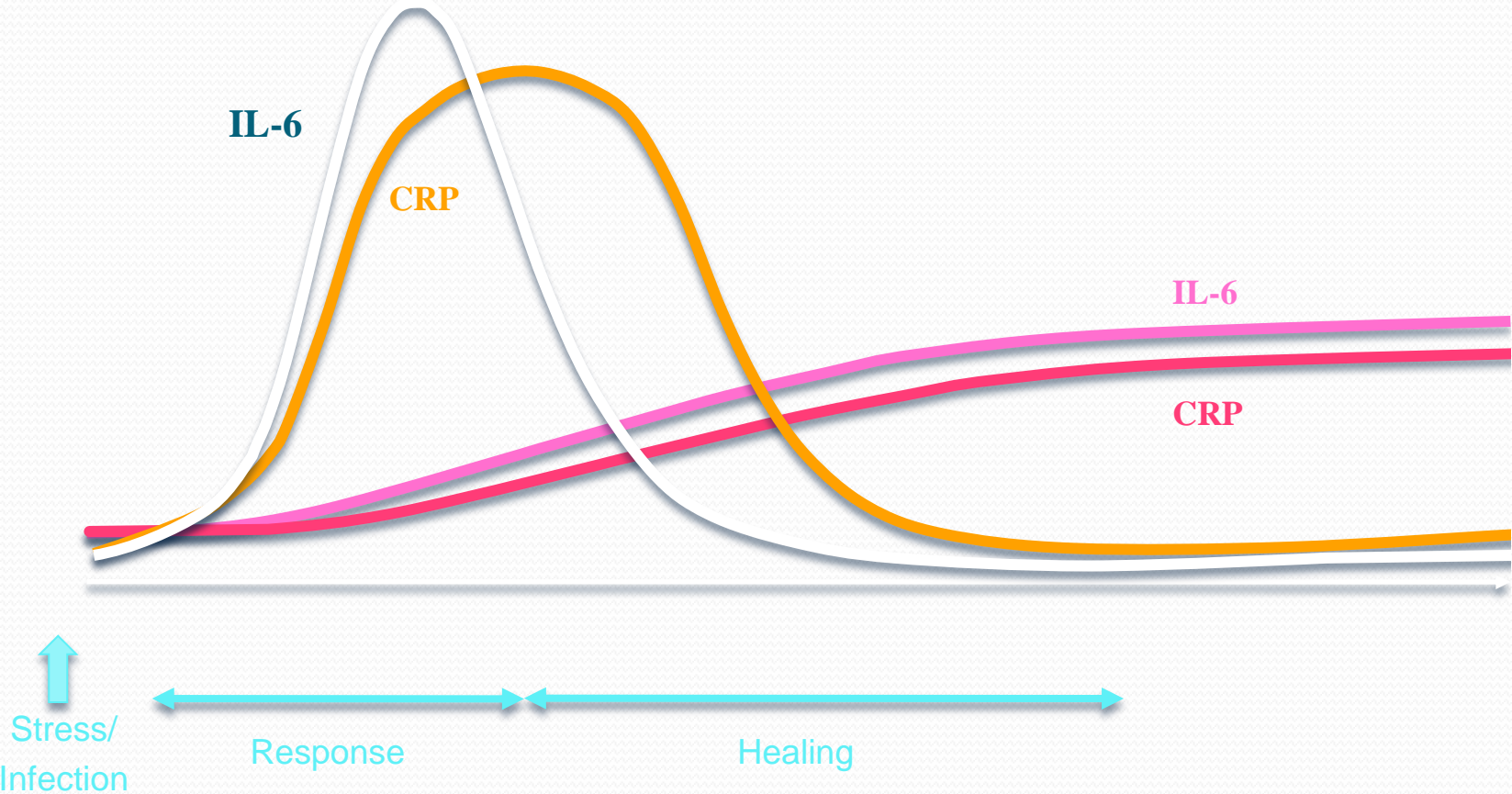
Introduction

- What is chronic inflammation?
- What triggers and sustains it?
- What are the consequences to the health of older adults?
- Can it be diagnosed and treated?

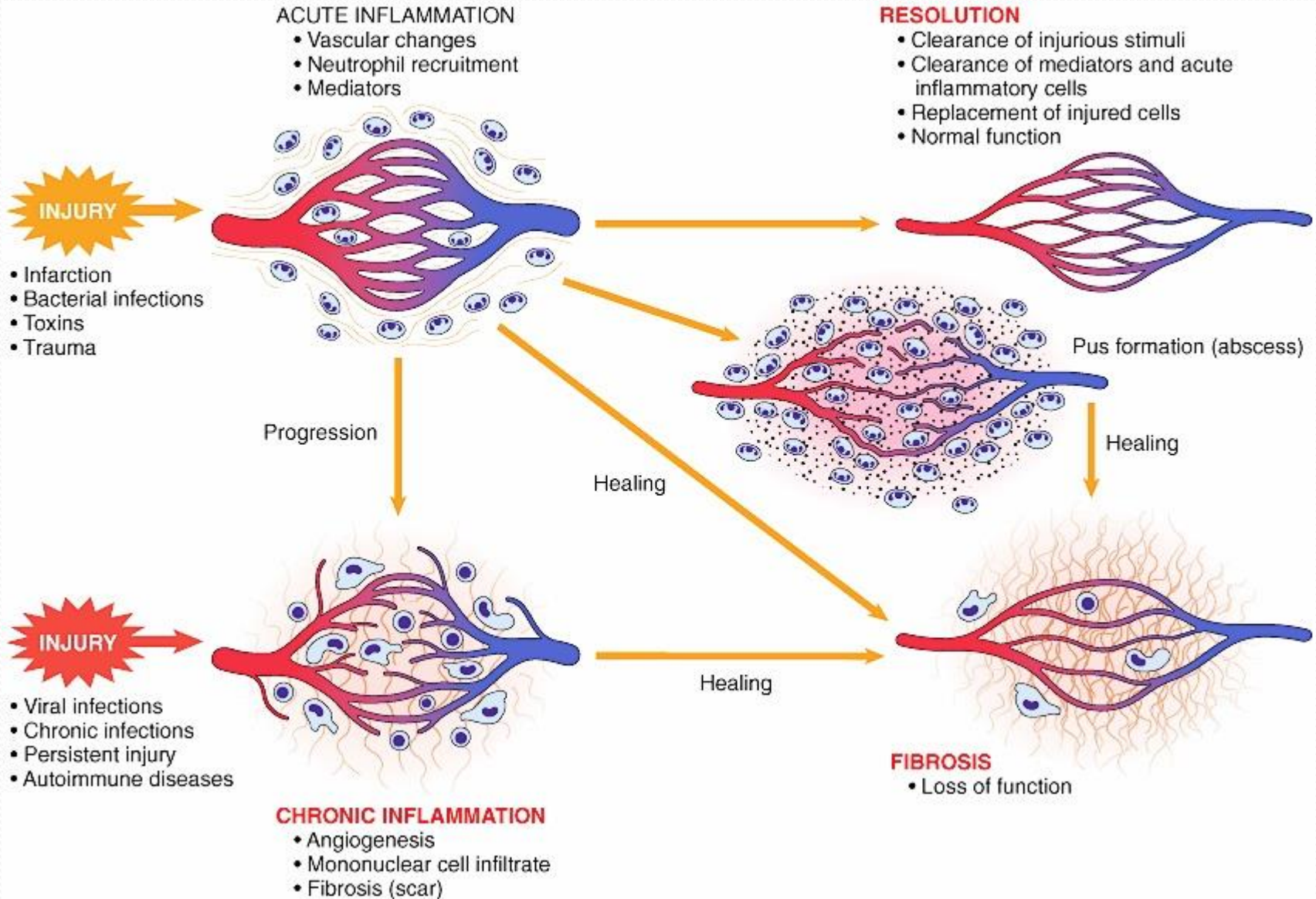
Chronic Inflammation

Age-related, multifactorial, low-grade activation of the innate immune system that leads to the chronic production of inflammatory mediators

Acute Vs. Chronic Inflammation Timeline

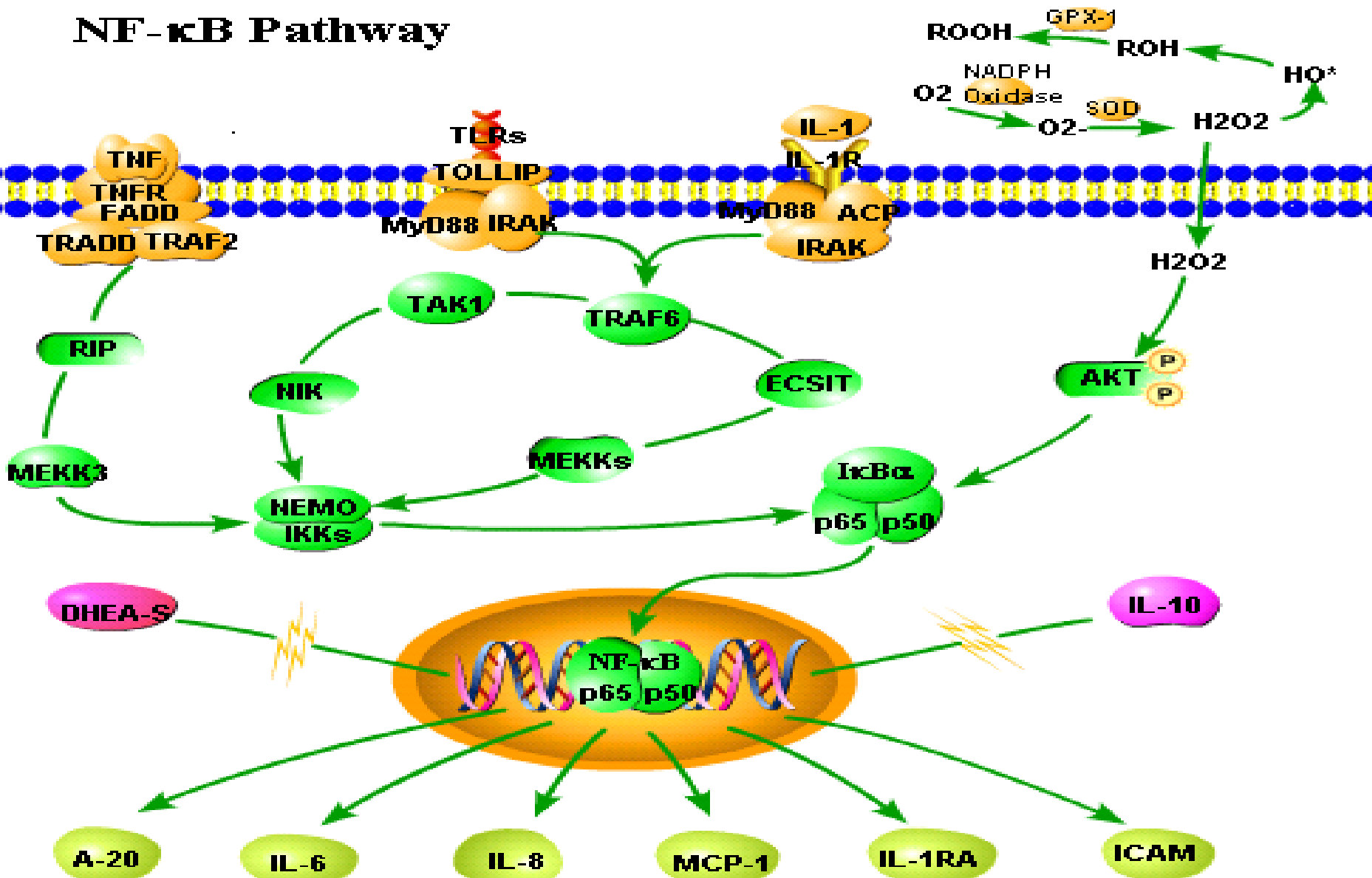


Inflammatory Response



Molecular Gateway to Inflammation

NF- κ B Pathway



Inflammatory Gateway: NFkB

TNF

IL-1

LPS

H₂O₂

NFkB

IL-6

IL-8

MCP-1

COX-2

fibrosis neutrophils apoptosis prostaglandins

Measuring Chronic Inflammation in Humans

- Usually done with serum markers
- Hundreds of association studies using mostly inflammatory cytokines as markers.
- Most tied to NF κ B pathways

Inflammatory Biomediators and Muscle Strength

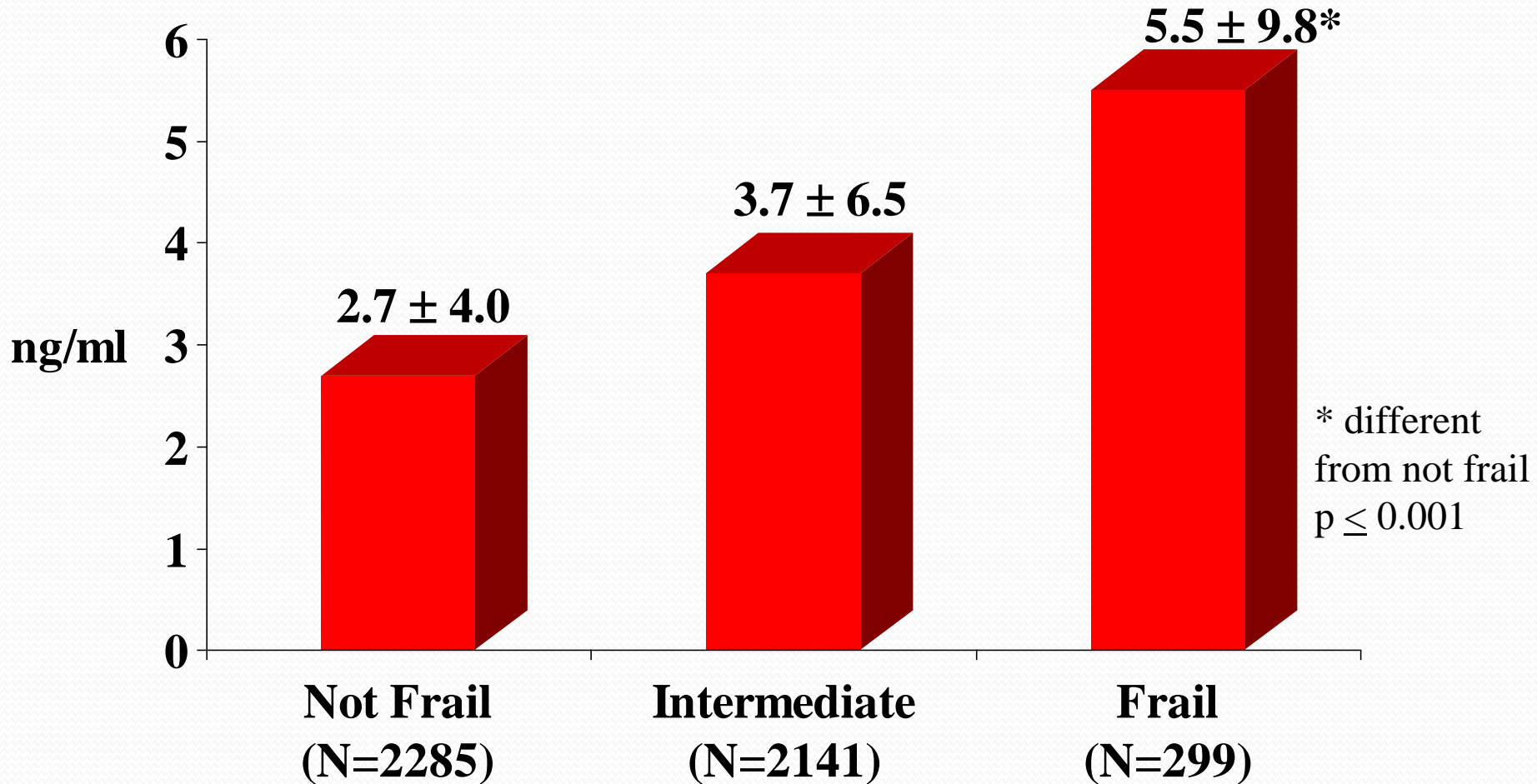
- In CHIANTI, n=1020, age 65-100
- CRP, IL-6, IL-1RA correlated with decreased performance and strength
- IL-6 most consistent biomediator

IL-6, CRP & Mortality

- IL-6 & CRP alone and in combination associate with mortality in healthy older adults.
 - IL-6 (>3.19 pg/ul) RR 2.1, (CI 1.3,3.4)
 - CRP (>2.78 mg/L) RR 1.7, (CI 1.1,2.6)
 - IL-6 & CRP RR 3.5, (CI 1.4-5.4)
- All cause and cardiovascular mortality rates not different

(Harris TB, et al., Am J Med. 1999)

C-Reactive Protein and Frailty



Inflammatory Biomediators and Muscle Strength

- Health ABC, n=3071, age 70-79
- Consistent relationship in all groups between IL-6 and lower strength
- TNF- α also significantly related to declines in strength in women

Best Serum Inflammatory Markers of Vulnerability

- IL-1 RA
- IL-6
- TNF-alpha R1
- IL-18
- CRP

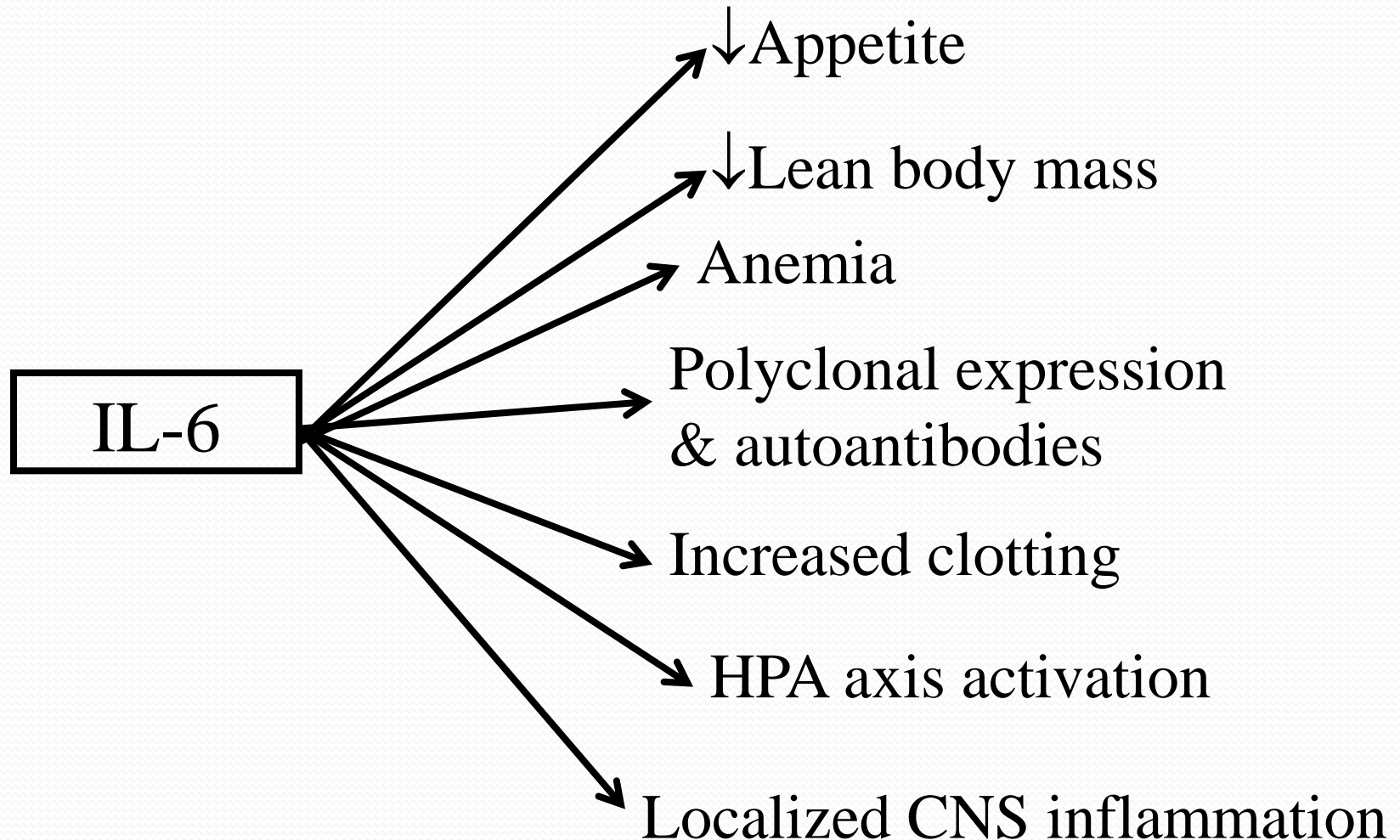
Inflammation Index and Mortality

Parameter	Chi-Square	Pr > ChiSq	Hazard Ratio
logCRP	72	<.0001	1.22
logIL6	287	<.0001	1.44
logTNFRI	274	<.0001	1.48
logIL18	24	<.0001	1.12
logIL1RA	56	<.0001	1.19
age	772	<.0001	1.80
WSS	281	<.0001	1.47
PCS	237	<.0001	1.43
IIS	433	<.0001	1.64

Varadhan R et al, JGMS, 2014.

Each predictor is adjusted by age, except age by its own

IL-6 and Multisystem Dysregulation



Chronic IL-6 Signaling

- Contributes to declines muscle satellite and blood stem cells
- Remodels immune system with senescent immune cell proliferation
- Drives mitochondrial dysfunction and fibrotic tissue changes
- Accelerates chronic disease

IL-6 and Multisystem Dysregulation

- Rhesus monkeys injected with low dose IL-6 developed multisystem changes
 - 10% lean body mass decline by DEXA within 30 days
 - Anemia & osteopenia
 - Decreased albumin & cholesterol
 - Increased CRP, alkaline phosphatase

Chronic TNF-Alpha R1

- Contributes to apoptosis and necroptosis signaling, and to accelerating cell loss
- Drives further inflammatory pathway activation and disease

What Triggers and Sustains It

- Senescent Fibroblasts/stromal cells
- Increased Fat Mass
- Damaged Mitochondria
- Altered Microbiome +Leaky Gut
- Diet, Lack of Exercise, Genes
- Chronic Disease and Chronic Infection

Dietary and Lifestyle Factors Associated with Inflammation

Increase Inflammation

Trans fatty acids
Saturated fatty acids
High glycemic index foods
Excessive alcohol
Smoking
Excessive exercise

Reduce Inflammation

Omega-3 fatty acids
Low cholesterol diets
Low glycemic index foods
Dietary fiber
Arginine-rich foods (fish, nuts)
Moderate alcohol intake
Physical activity

Do Stress Response Systems Underlie Vulnerability?

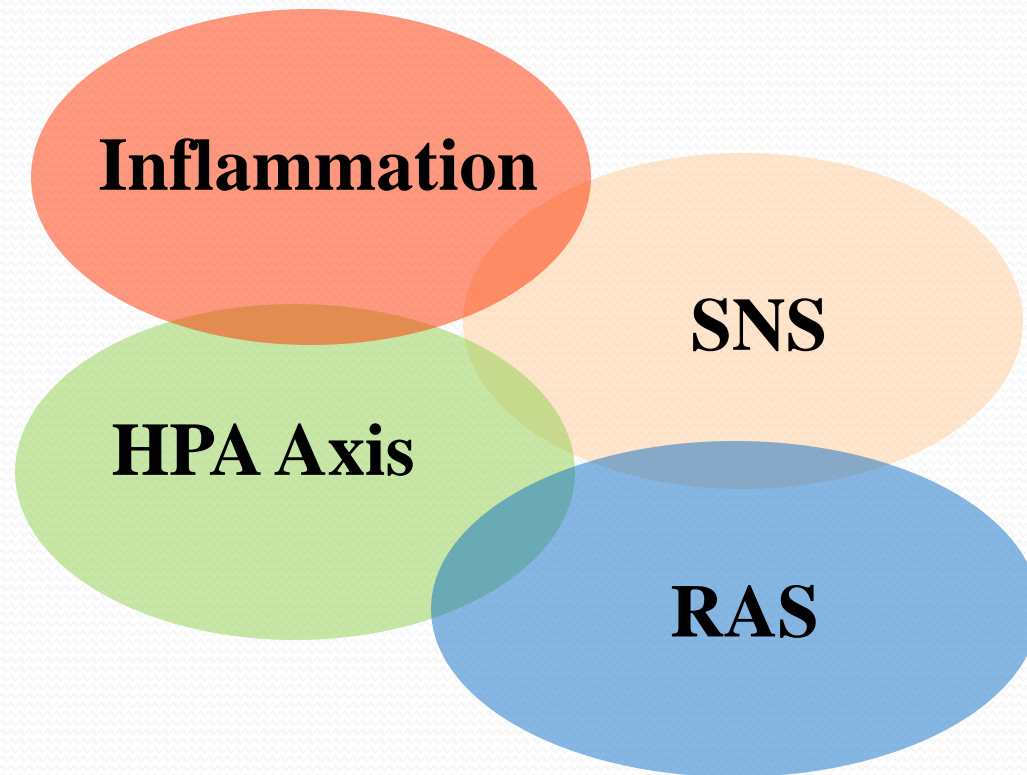
Inflammation

SNS

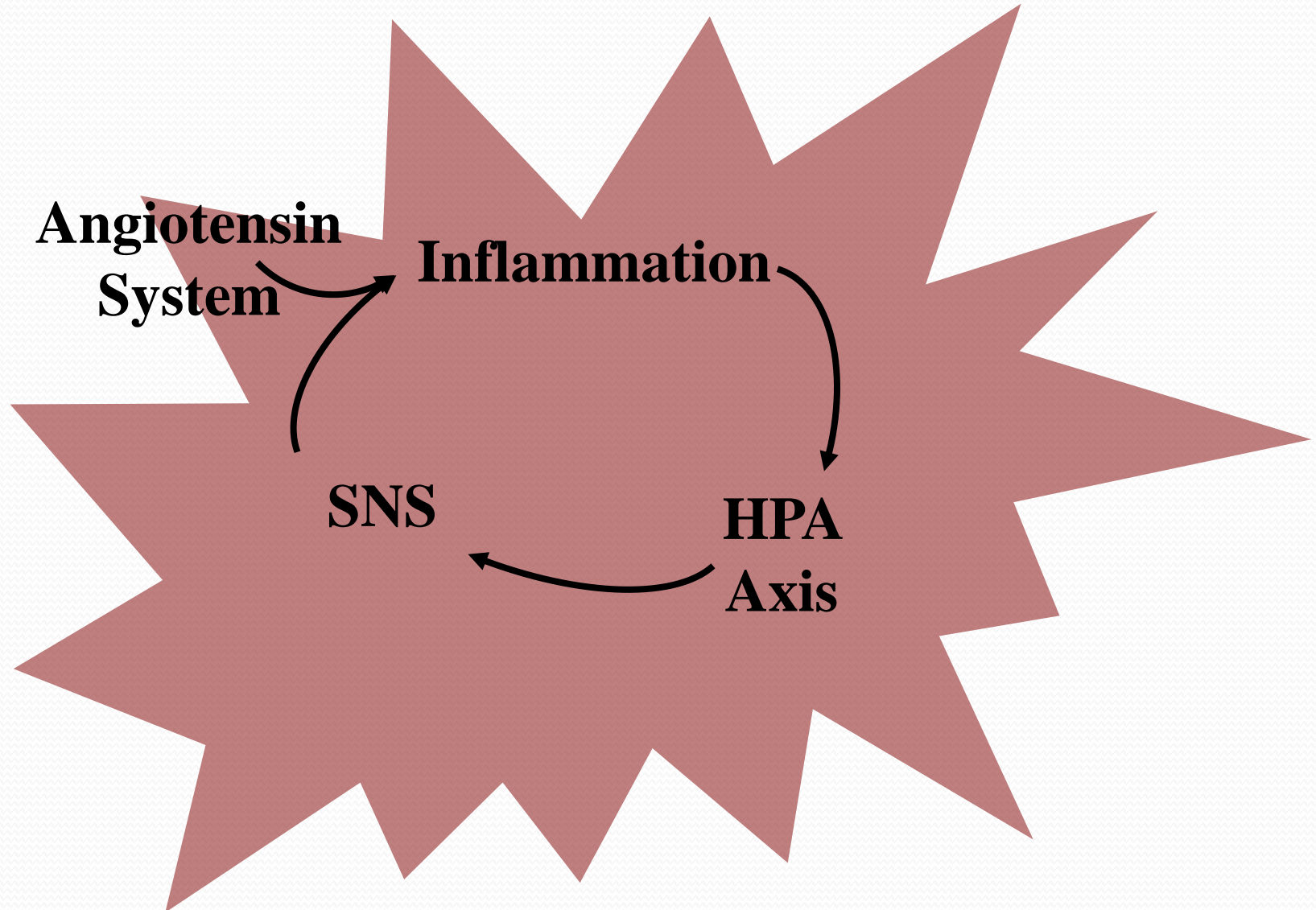
HPA Axis

RAS

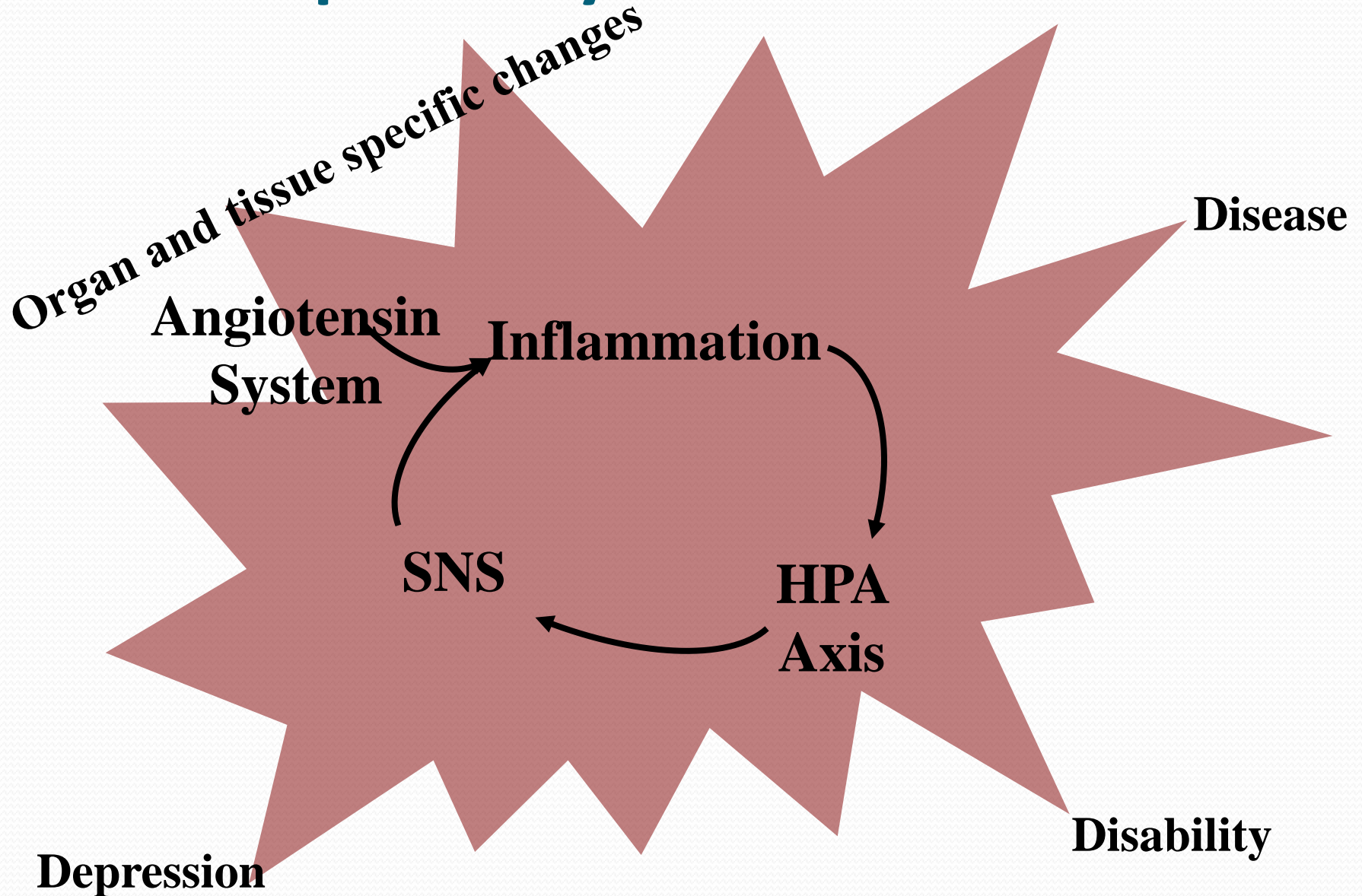
Key Stress Response Systems



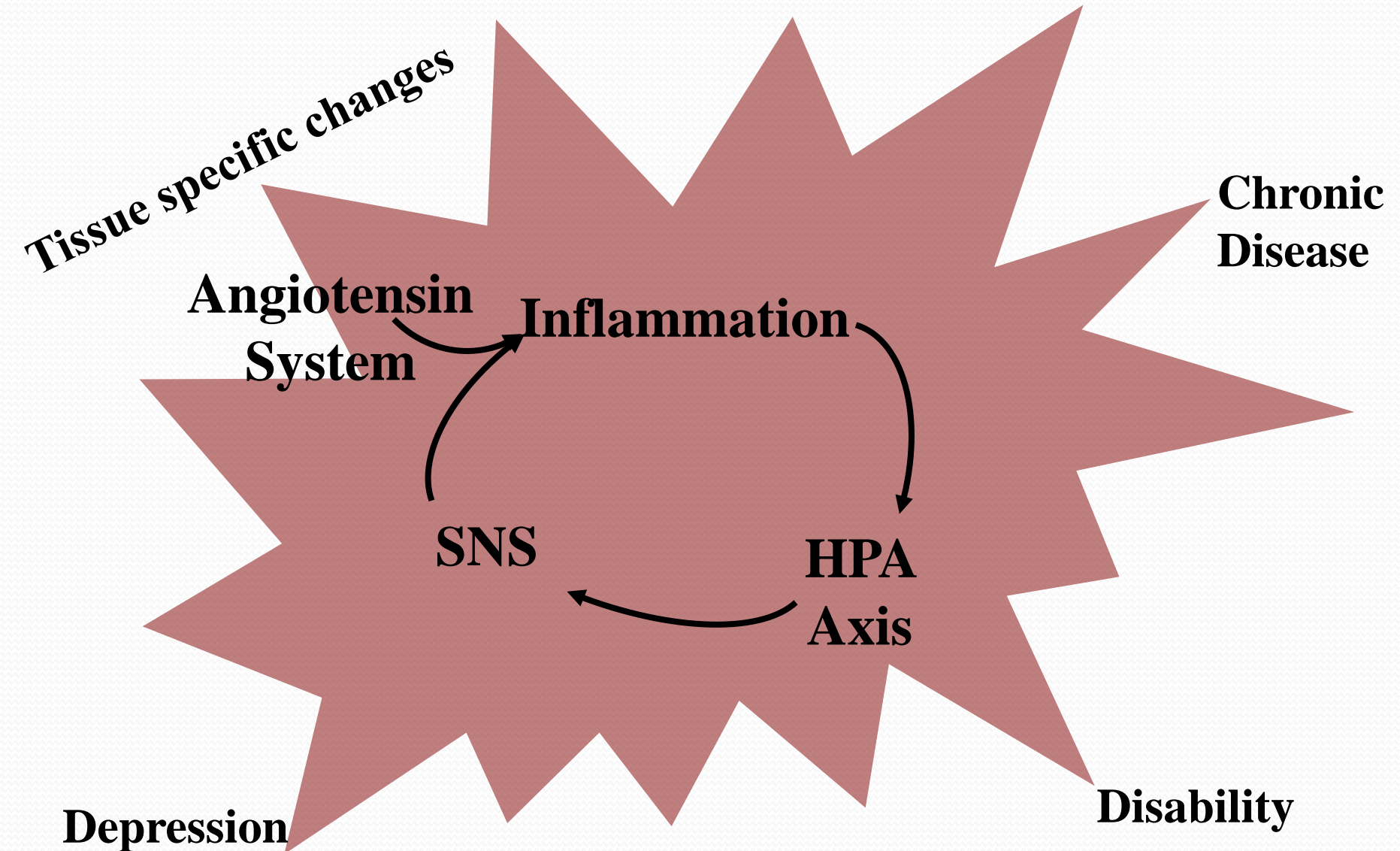
Stress Response Systems and Vulnerability



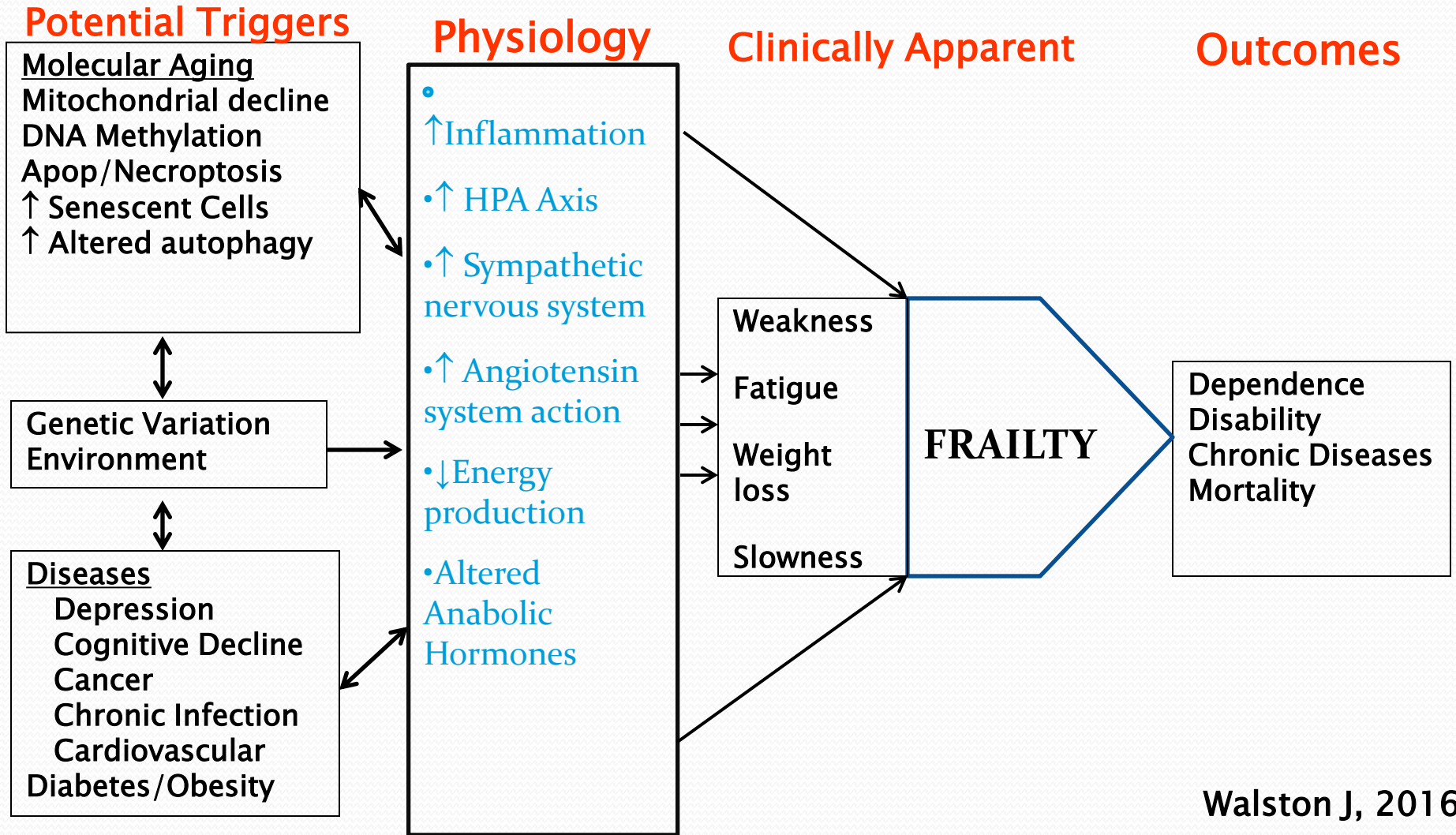
Stress Response Systems and Vulnerability



Stress Response Systems and Vulnerability



Model Pathway to Frailty and Adverse Outcomes in Older Adults



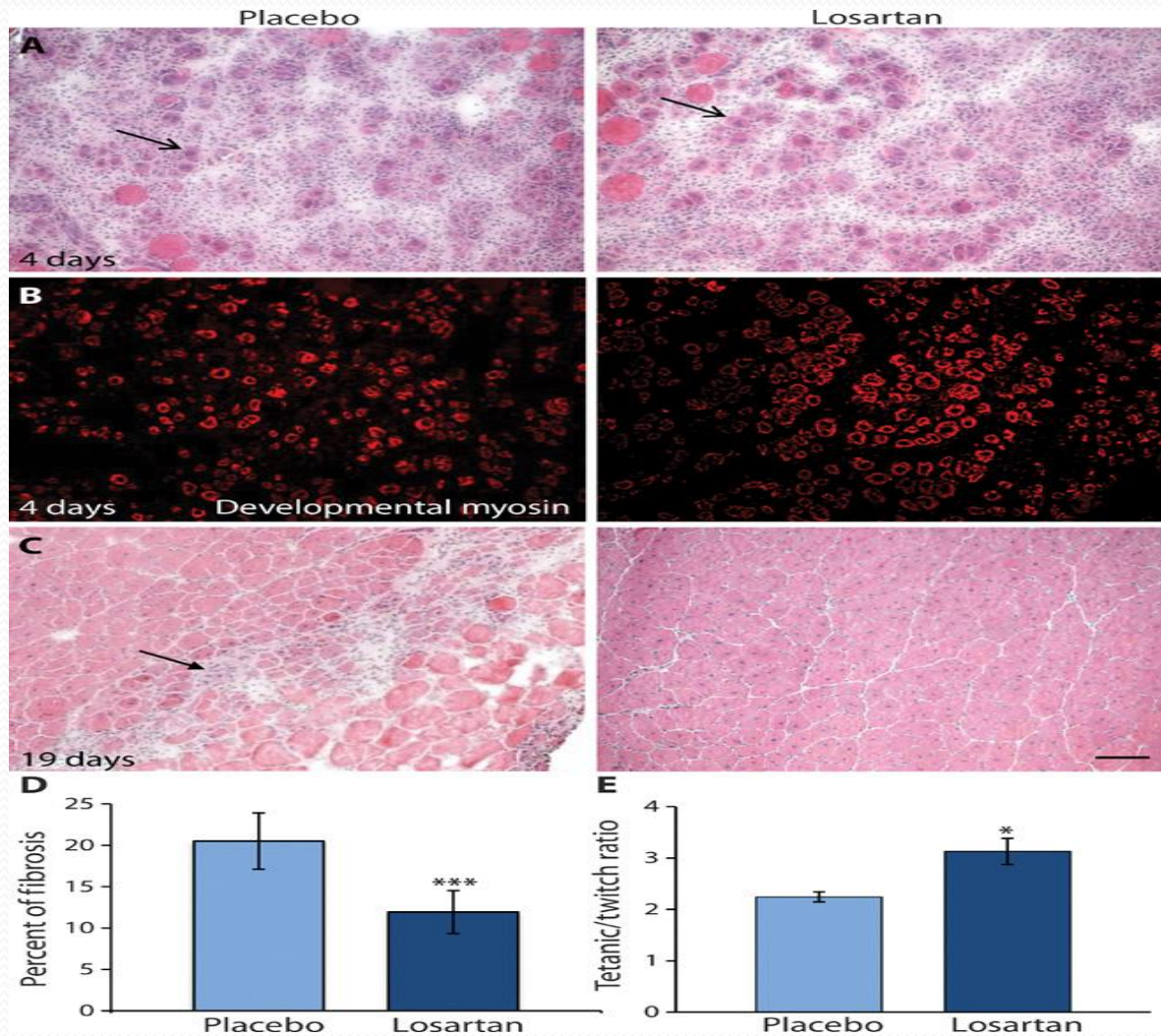
Tried and True Interventions that Reduce Inflammation

- EXERCISE
- EXERCISE
- EXERCISE
- GOOD NUTRITION
- Ongoing research looking into best types of activities and into optimal nutritional needs of older adults (ie. types of protein that may be of most benefit).

Novel Interventions to Reduce Inflammation

- Angiotensin Receptor Blockers Being studied (Hopkins OAIC and ENERGISE)
- Other drugs such as NSAIDs not safe to utilize in chronically ill older adults
- Dietary supplements
 - Omega 3 fatty acids
 - Antioxidant derivatives of 'superfoods'
 - Lactoferrin

Losartan Improves Muscle Remodeling and *in vivo* Function in Older Mice



Future Directions

- Development of Best Clinical Measurement for Diagnostic and Treatment Monitoring Purposes
- Identify Specific ‘Upstream’ or causal measurements
- Determine ‘Downstream’ or reactive measurements and their impacts

'Upstream' or Causal Measures

- Specific Need for
 - Leaky Gut Markers
 - Mitochondrial Dysfunction Markers
 - Senescent Cell Markers
 - Altered Microbiome Markers
 - Early and stable inflammasome activation detection

'Downstream' Measures with Consequences

- Kynurine and neurotoxic derivatives
- Energy Metabolism (mitochondrial) Measures
- Remodulated or senescent immune system markers
- Altered Mitochondrial Function Markers
- (metabolomic and/or proteomic approaches may be helpful here)

Acknowledgments

JOHNS HOPKINS UNIVERSITY

✿ **OLDER AMERICANS** ✿

INDEPENDENCE CENTER

• <http://www.jhsph.edu/research/centers-and-institutes/johns-hopkins-center-on-aging-and-health/oaic/>