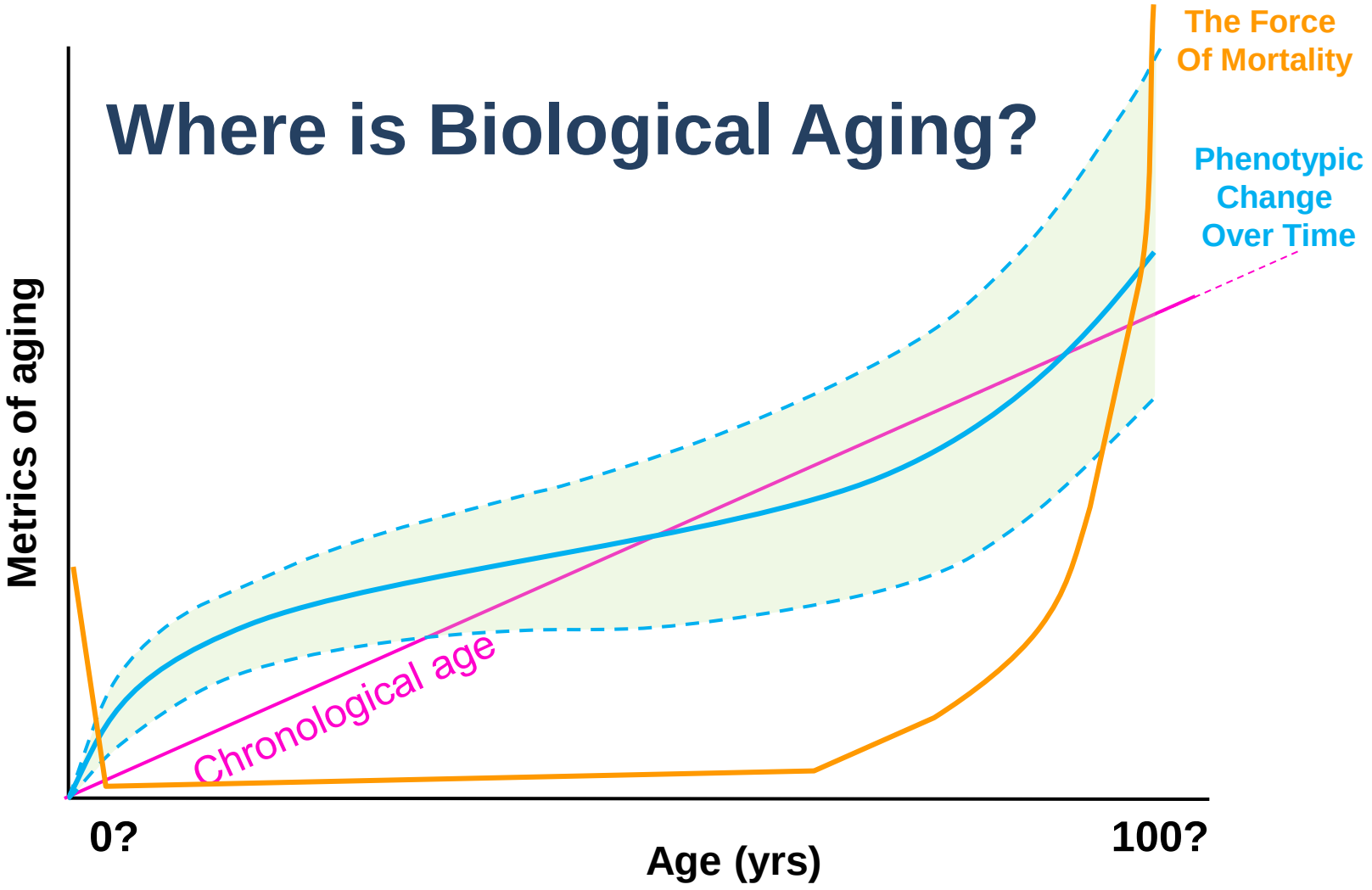
Nutrition Across the Lifespan for Healthy Aging
Food Forum Workshop

September 13-14, 2016
The National Academies of Sciences Building, Lecture Room
2101 Constitution Avenue, NW, Washington, DC

Biomarkers of Aging

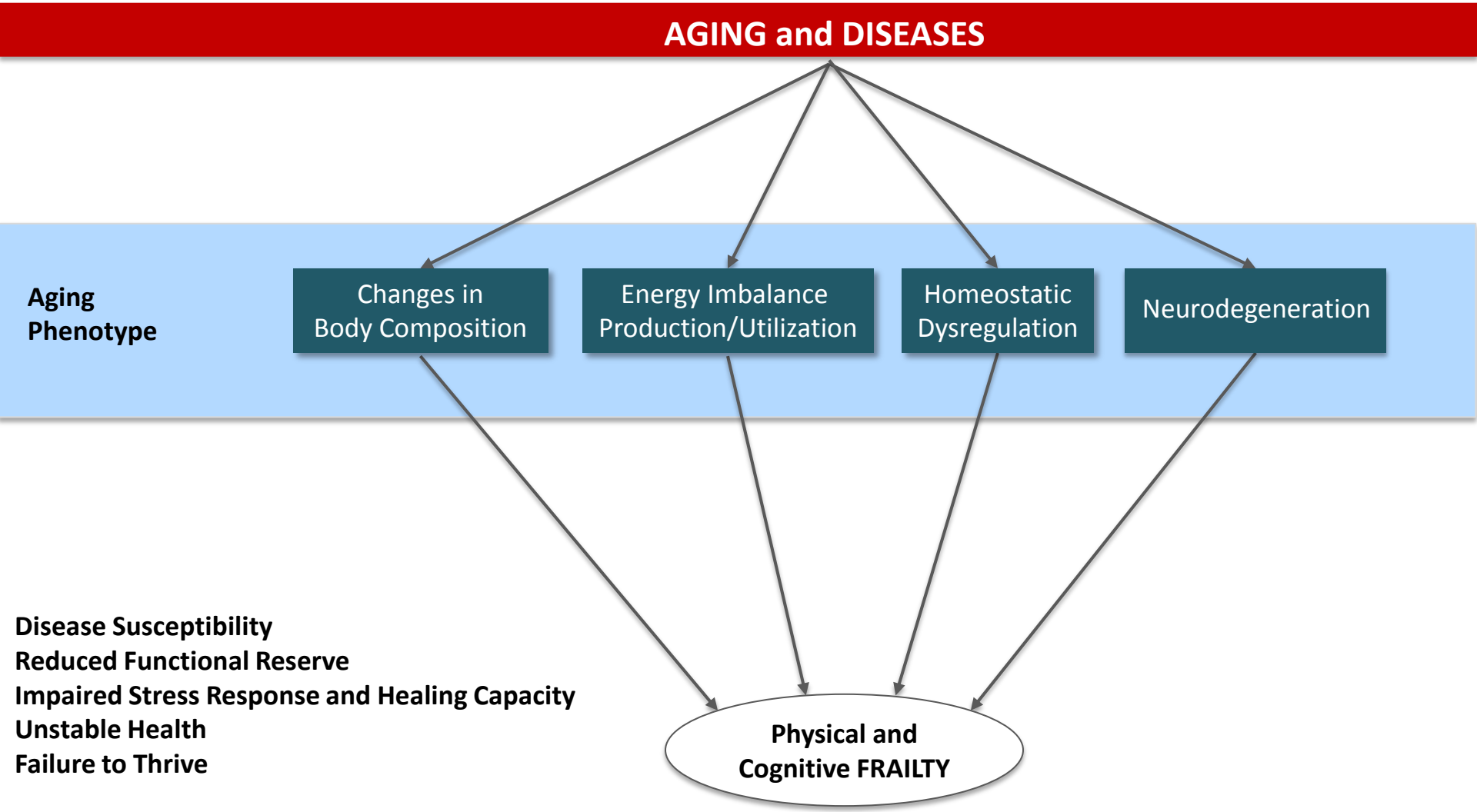
Luigi Ferrucci
National Institute on Aging

Discrepancy Between Biological and Chronological Age




BAR Caffè
RISTORANTE PIZZERIA ALLA SPERANZA
RISTORANTE PIZZERIA "LA COSTA"
BAR GELATERIA

Domains in the Causal Pathway to Cognitive and Physical Frailty



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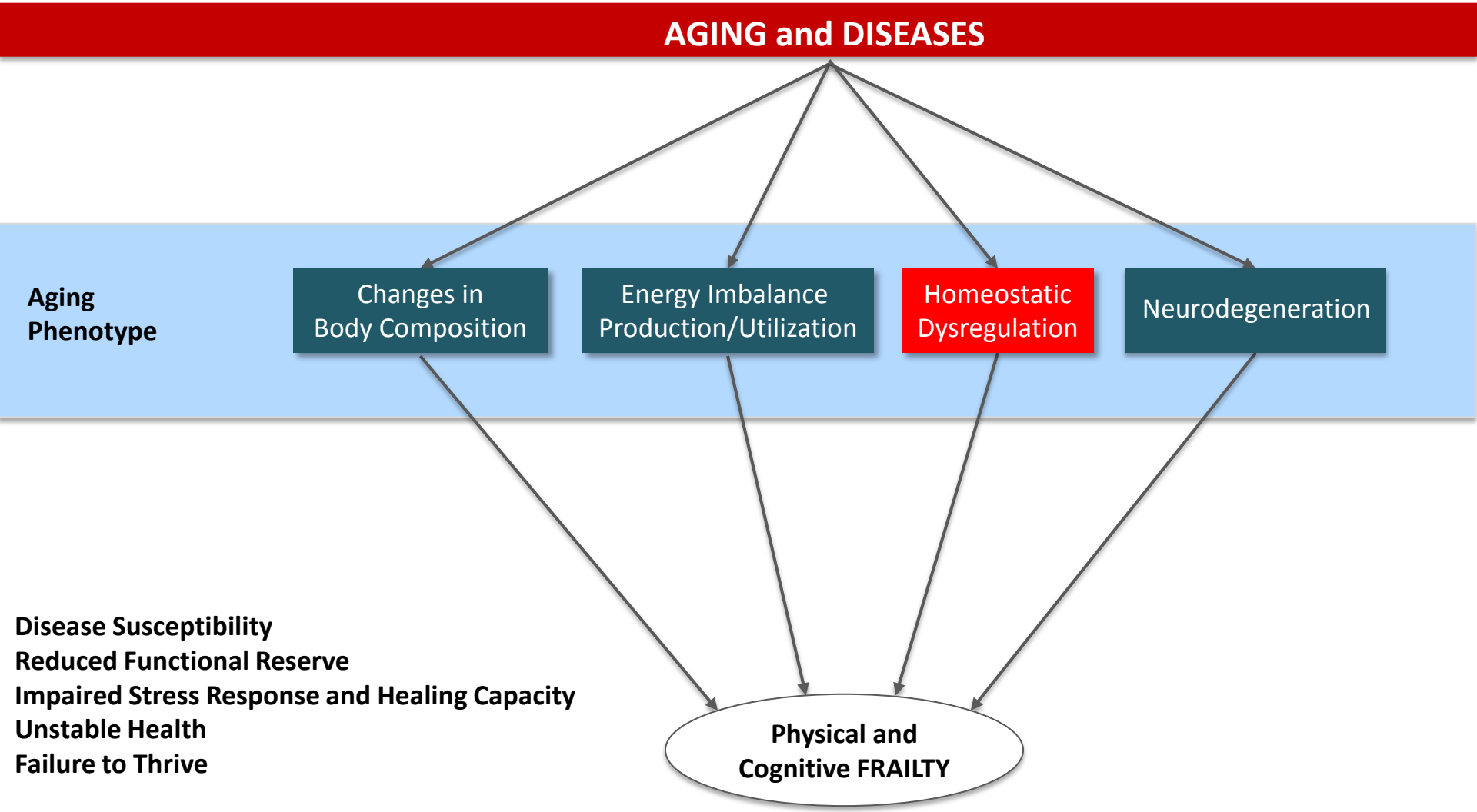

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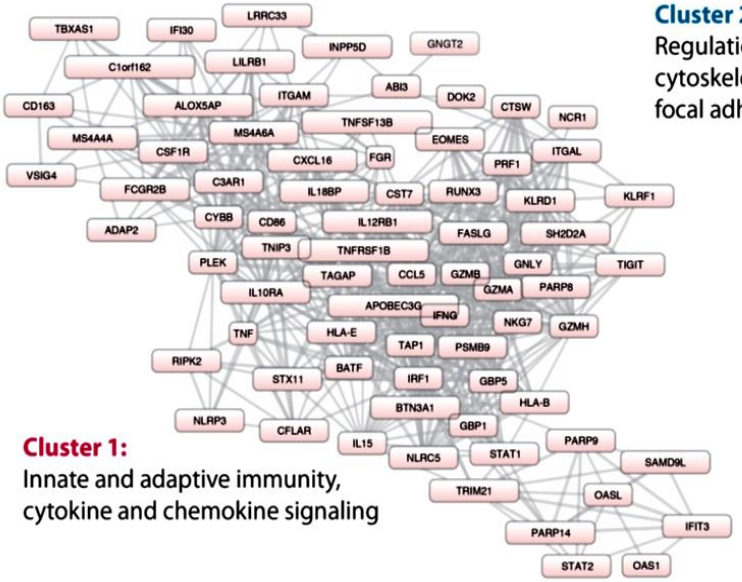
Genes up-regulated with aging

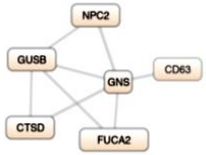


Cluster 1:
Innate and adaptive immunity, cytokine and chemokine signaling

Cluster 2:
Regulation of actin cytoskeleton, focal adhesion

Cluster 3:
Fatty acid metabolism, peroxisome activity

Cluster 4:
Lysosome metabolism and glycosaminoglycan degradation

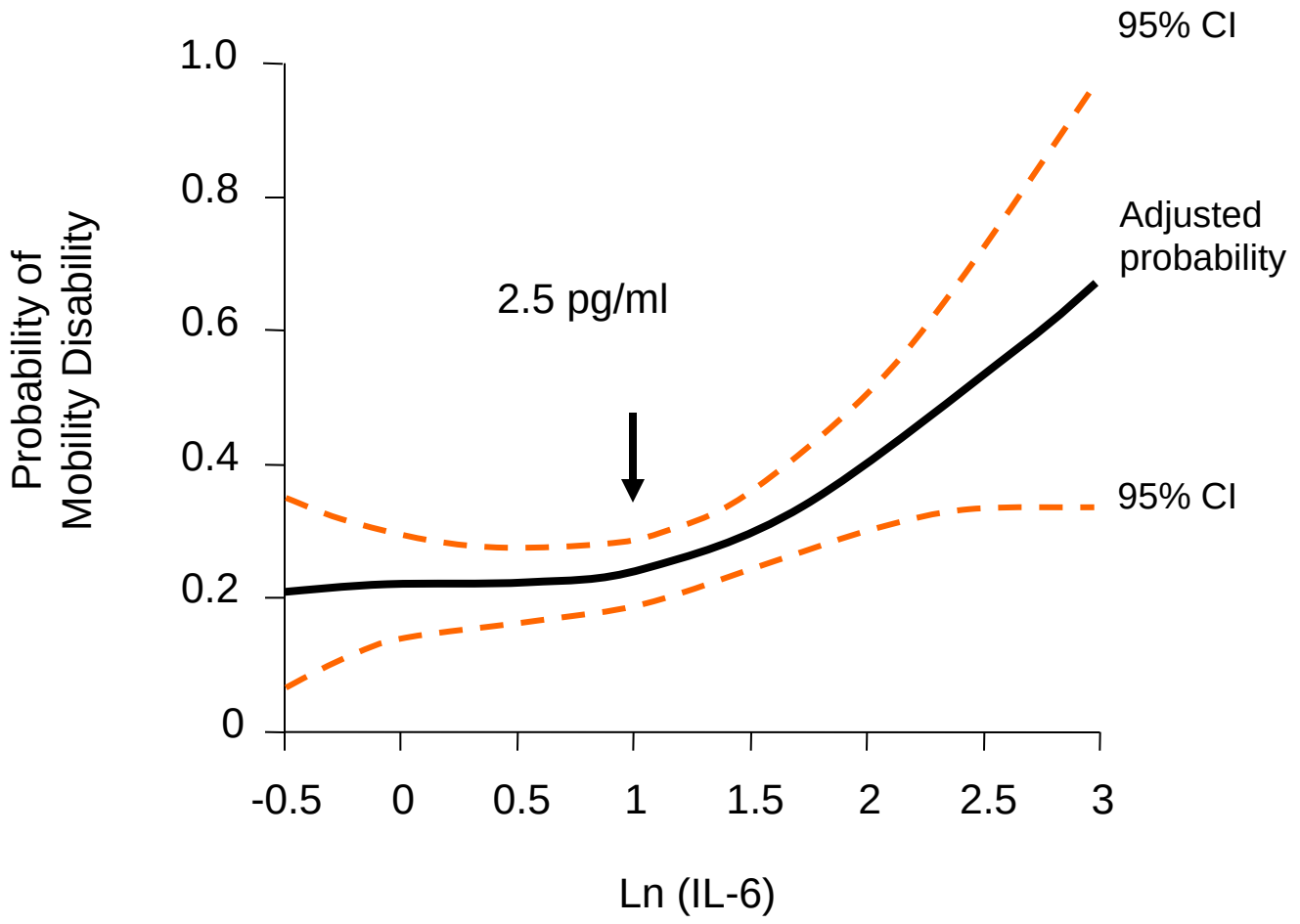


Aging is associated with up-regulation of immune function genes.

Transcriptome-wide meta-analysis of genes whose expression differs by age in 7,257 individuals of European ancestry. Findings replicated in another 8,009 individuals. 1,497 genes were differentially expressed with age. The major cluster of positively age-correlated genes (GeneNetwork pathway, 77 genes) was related to **innate and adaptive immunity**, suggesting that dysregulation of the immune leading to a pro-inflammatory state is an hallmark of aging.

Interleukin-6 Serum Levels Predict Incident Disability

A Case Cohort Study Nested in the EPESE



Ferrucci et al. *JAGS 1999;47: 639-44*

Systemic Effects of Localized Inflammation

Harmful stimuli:
- Damaged cells
- Irritant chemicals
- Pathogens

INFLAMMATION attempts to remove damaged cells, irritants or pathogens

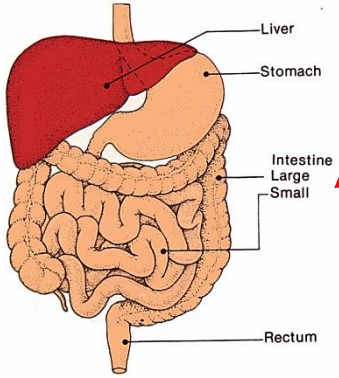
Effective Eliminates the cause of inflammation

"Switch off" inflammation

Healing

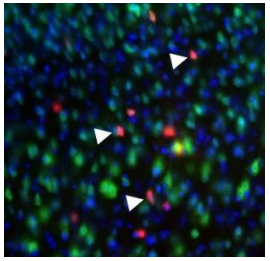
Systemic Effects

G.I. System



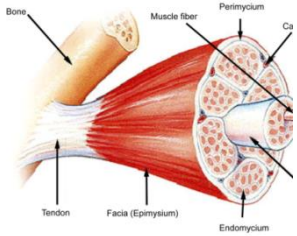
- Reduces food absorption
- Causes insulin resistance
- Stimulates glycogenolysis
- Down-regulates somatostain

Brain



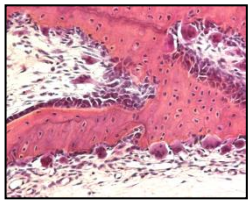
- Activates microglia
- Inhibits Neurogenesis
- Down-regulates BDNF

Muscle



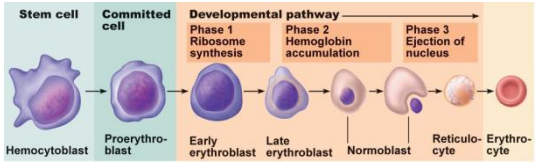
- Inhibits muscle growth
- Down-regulates IGF-1 signaling

Bone



- Stimulates osteoclasts
- Down-regulates Osteocalcin

Bone Marrow



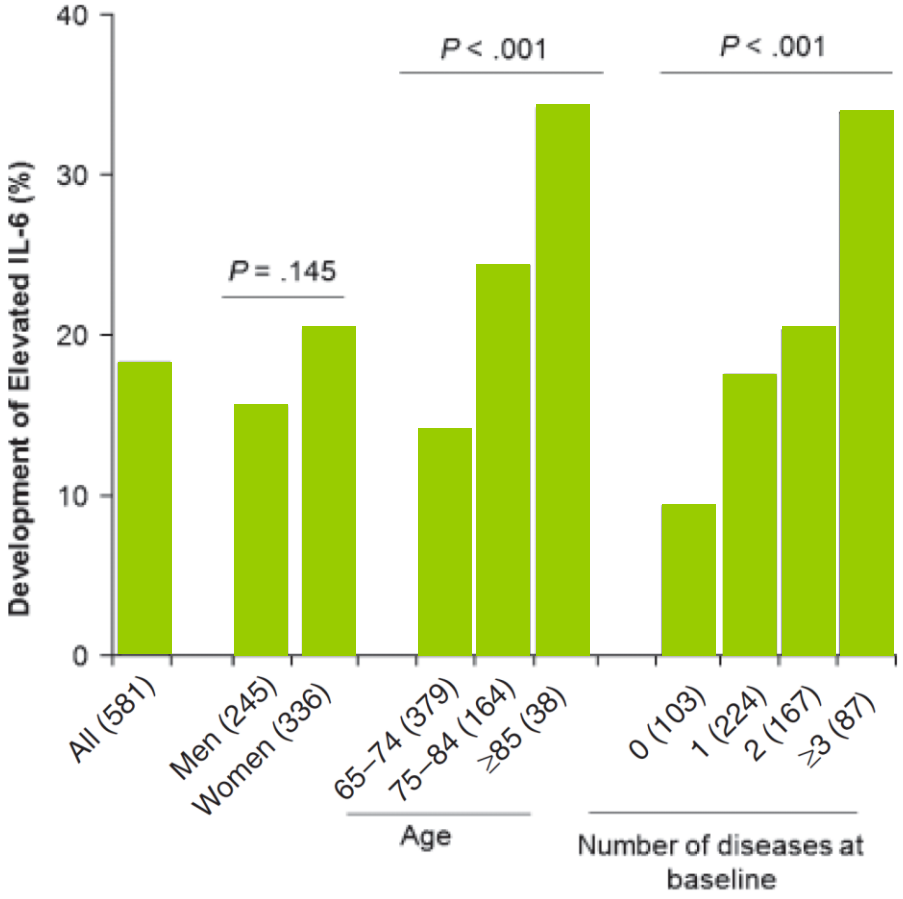
- Inhibits Hematopoiesis
- Down-regulates EPO signaling

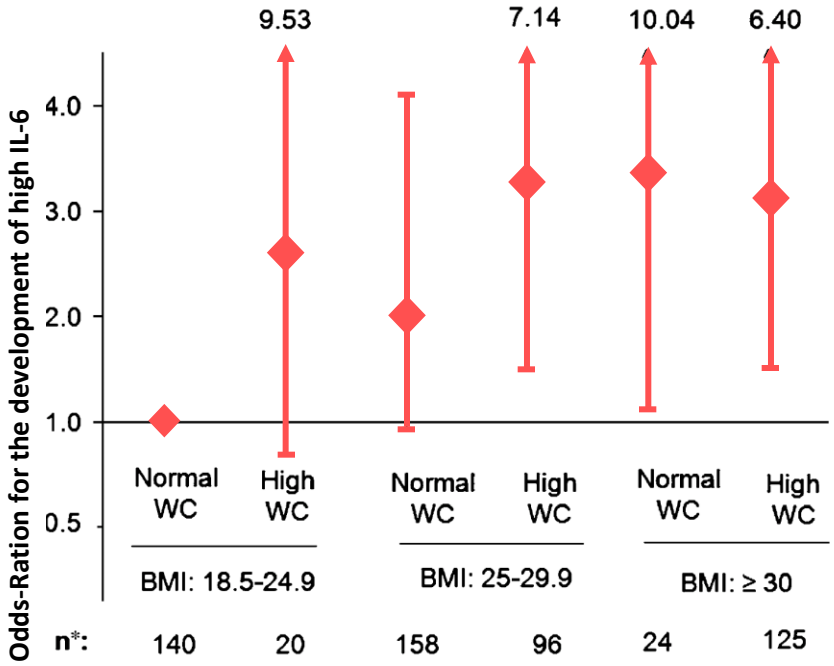
Arteries

- Stimulates atherosclerosis
- Inhibit endothelial reactivity

Predictors of Interleukin-6 Elevation in Older Adults

Shuhan Zhu, BS,[*†] *Kushang V. Patel, PhD, MPH,*[†] *Stefania Bandinelli, MD,*[‡] *Luigi Ferrucci, MD, PhD,*[§] *and Jack M. Guralnik, MD, PhD*[†]





J Am Geriatr Soc 2009.

Surgery

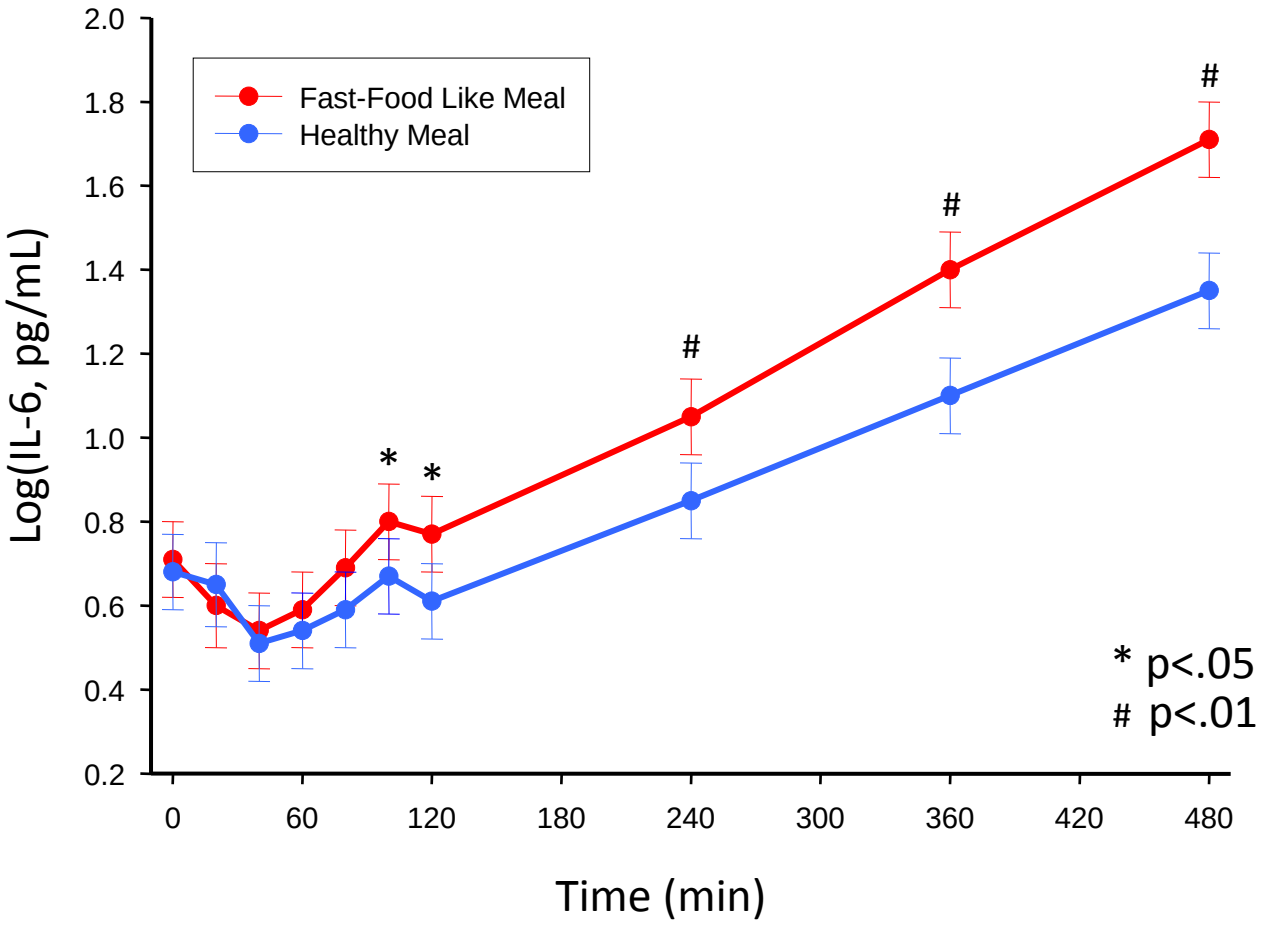
- Bariatric surgery
- Proven to prevent diabetes
- Weight loss ~ 30%
- Several studies
- Consistently reduces markers of inflammation before any weight loss

- Liposuction
- Fewer reports
- Even with 10 kg liposuction, no change in metabolic parameters and inflammatory markers

eg. Klein *et al*, NEJM 2004

The Fast Food Study

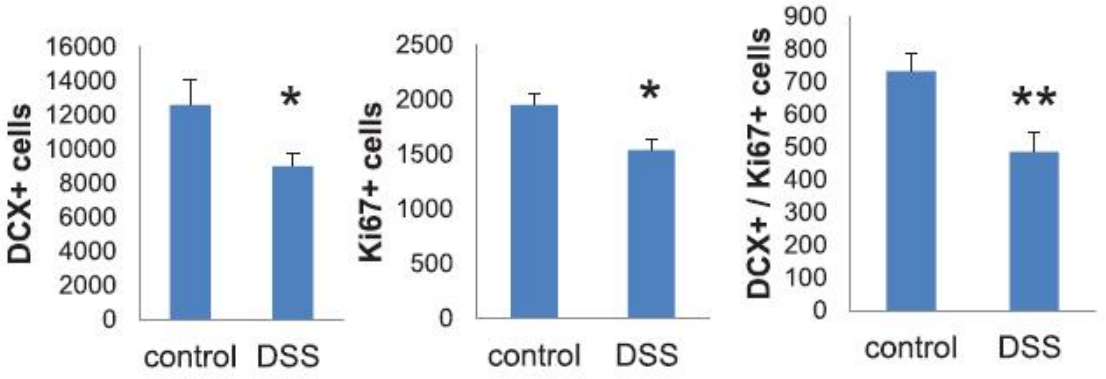
Change Over Time in IL-6 According to Meal Type

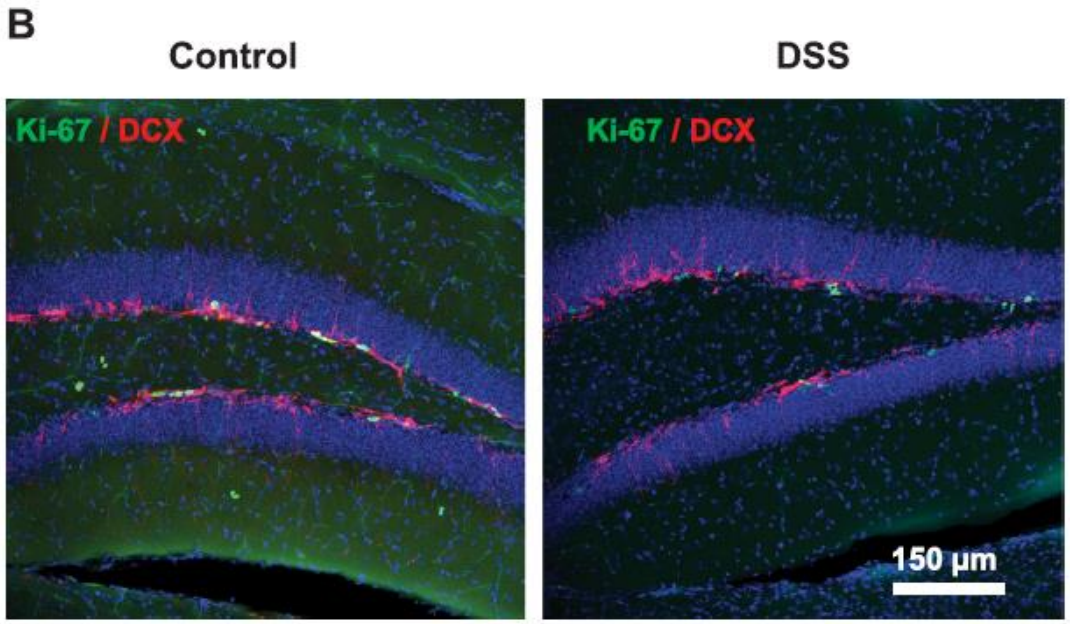


Fat

Chronic intestinal inflammation alters hippocampal neurogenesis

Svetlana Zonis et al. Journal of Neuroinflammation (2015) 12:65

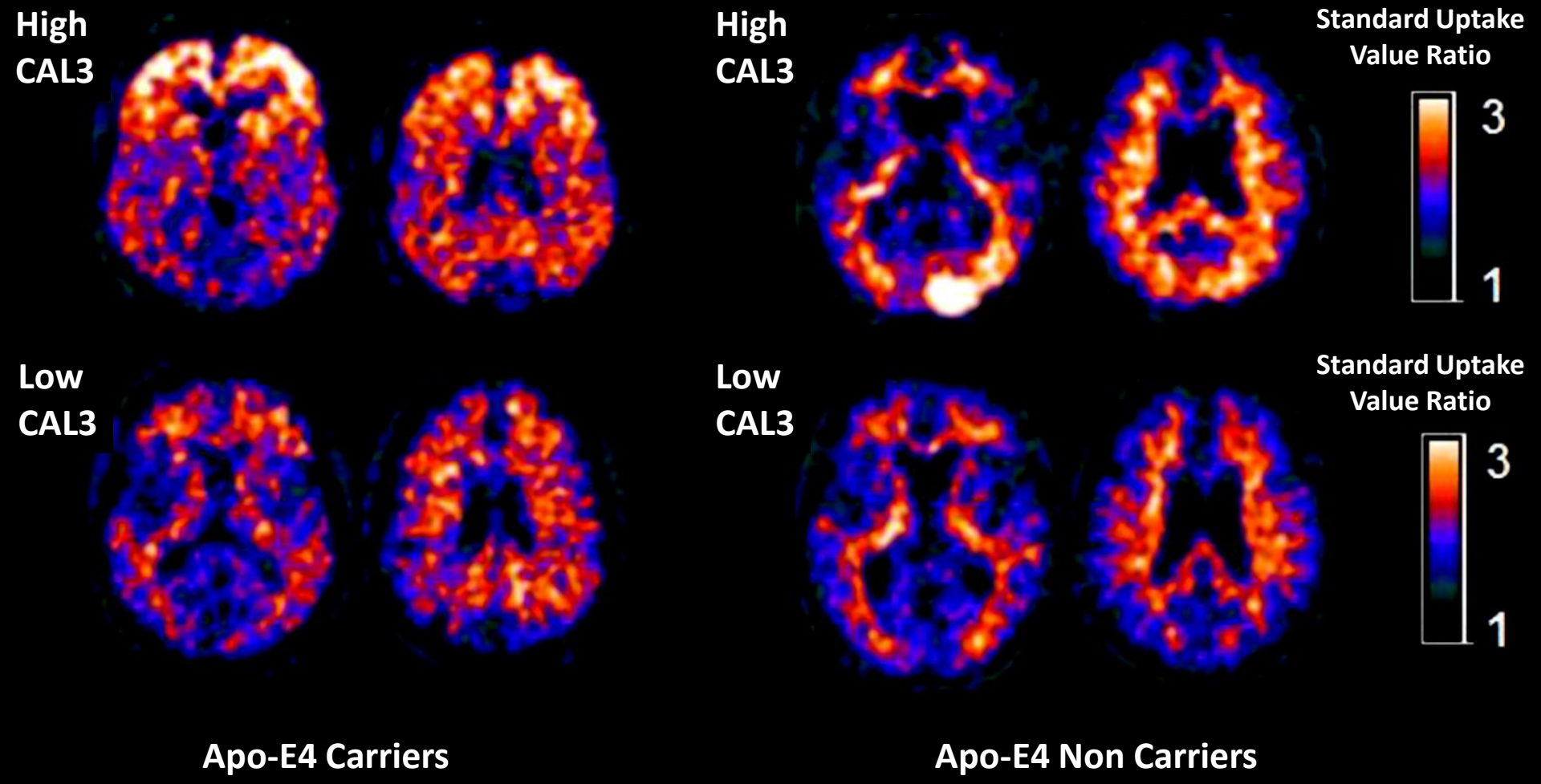




DSS=Dextran Sodium Sulphate; DCX=cytoplasmic marker doublecortin; Ki-67= nuclear, green

Periodontal disease associates with higher brain amyloid load in normal elderly

Angela R. Kamer et al. Neurobiol Aging. 2015 February ; 36(2): 627–633



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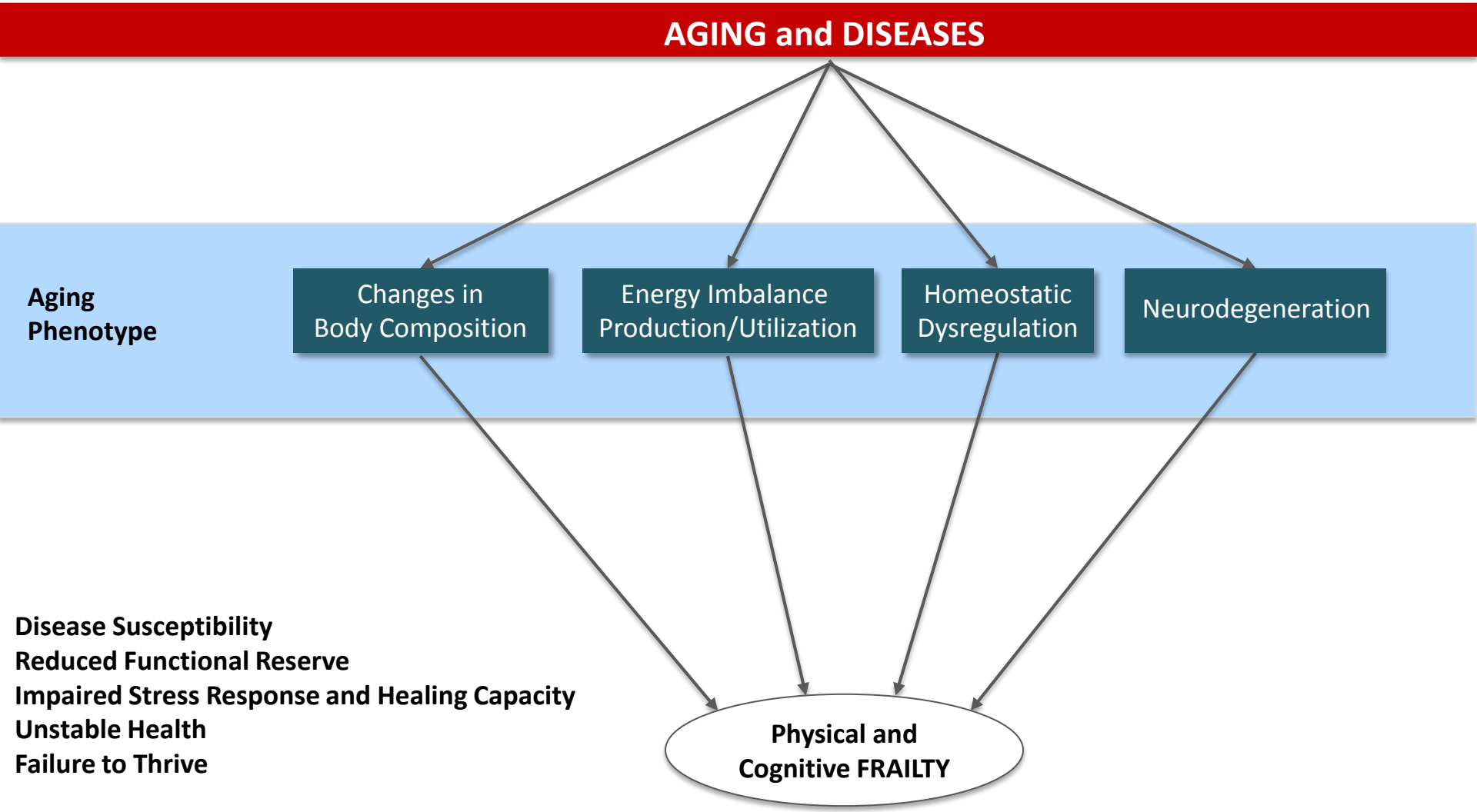

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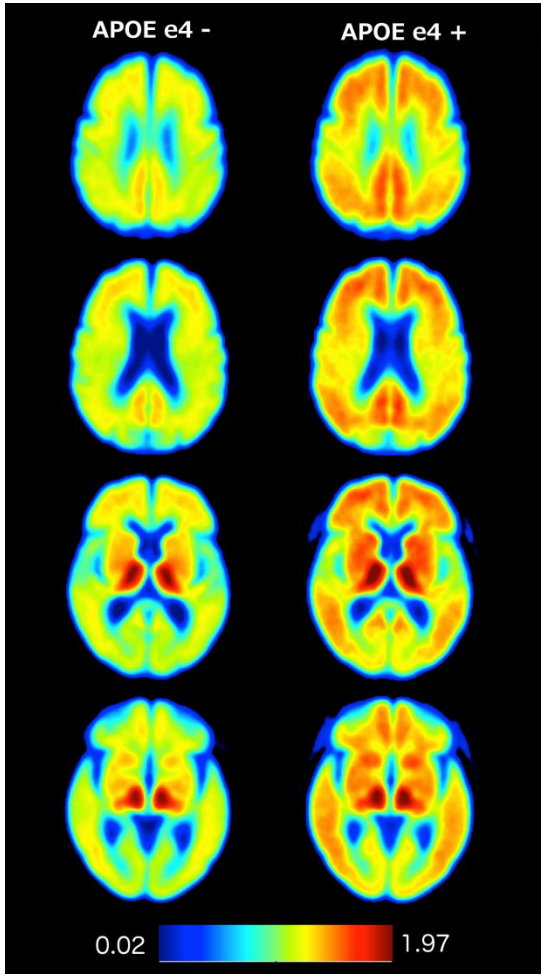
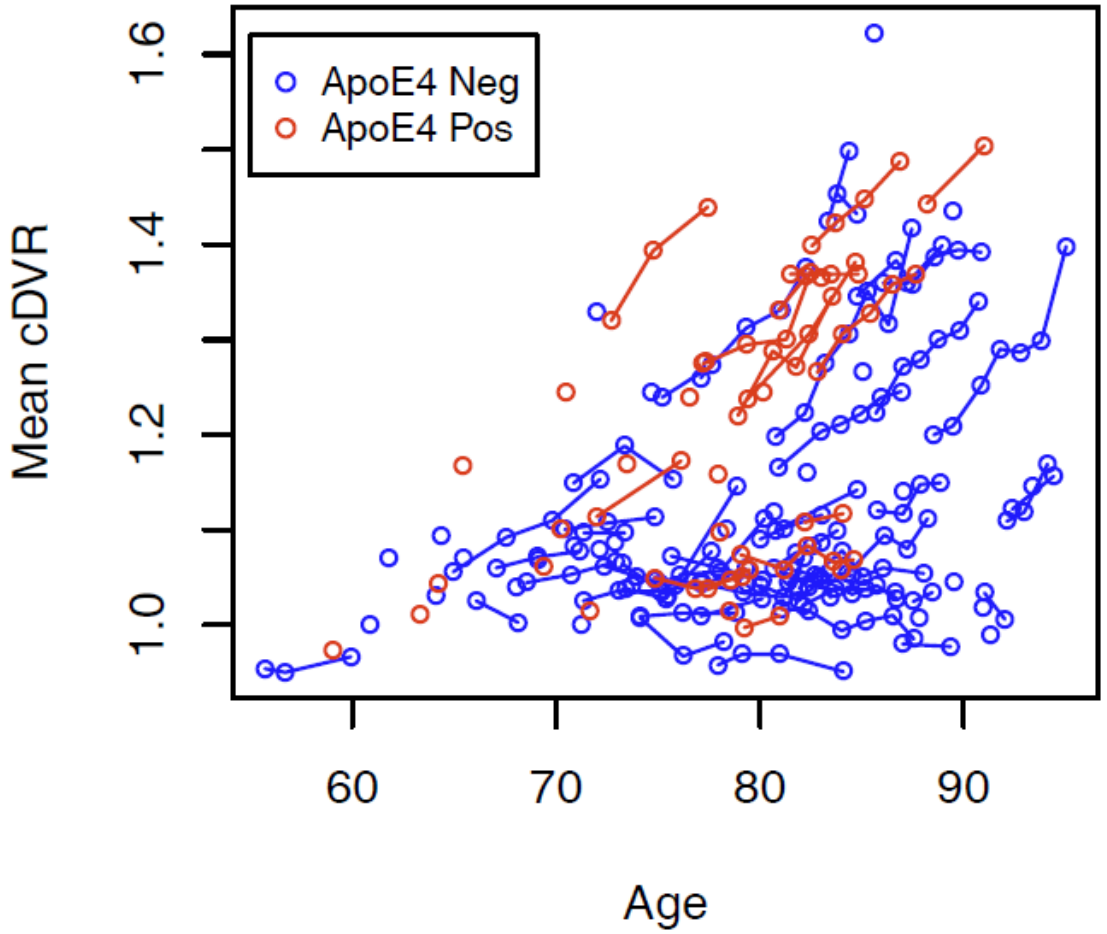
Genetics: APOE Genotype Affects Baseline Amyloid Burden But Not Rate of Change



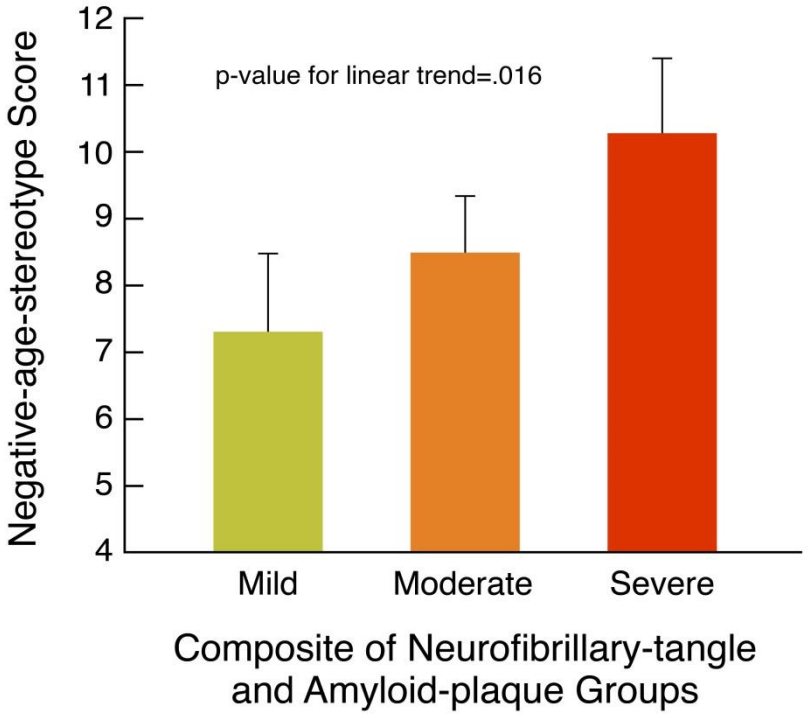


Susan Resnick, LBN/NIA

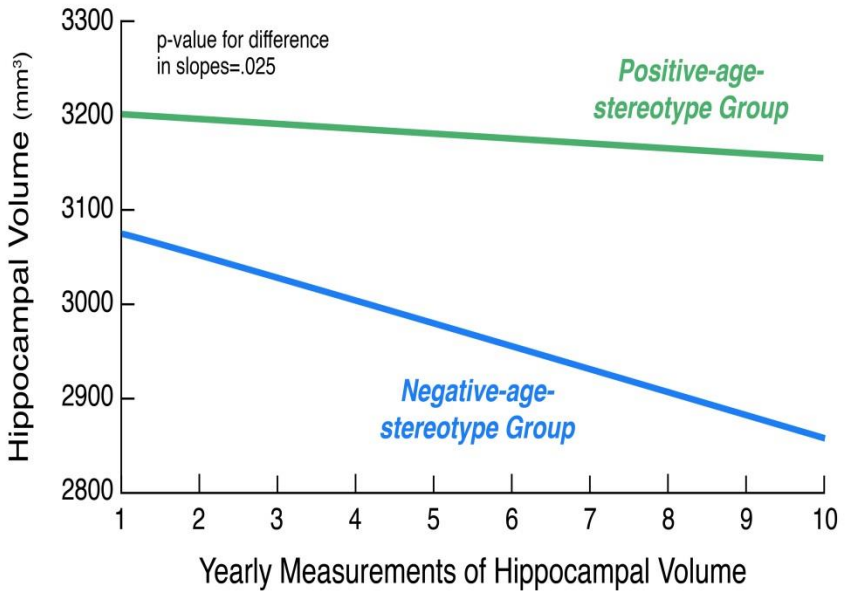
A Buffer against Chronic Stress:

Positive Aging Self-stereotypes Predict Reduced Cortisol over Time

Becca R. Levy, Scott Moffat, Susan M. Resnick, Martin D. Slade, and Luigi Ferrucci



Association of Age Stereotypes with AD Neuropathology at Autopsy



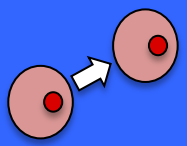
Association of Age Stereotypes with Hippocampal-Volume Decline over Time

What are the mechanisms by which aging and disease affect aging phenotypes and longevity?

AGING and DISEASES

Stem Cells Exhaustion

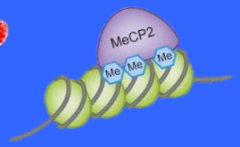
Altered Intercellular Communication



Genomic Instability

Telomere Attrition

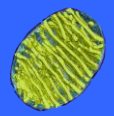
Epigenetic Alterations



Loss of Proteostasis

Deregulated Nutrient Sensing

Mitochondrial Dysfunction



Cellular Senescence

Aging Phenotype

- Changes in Body Composition
- Energy Imbalance Production/Utilization
- Homeostatic Dysregulation
- Neurodegeneration

Disease Susceptibility
Reduced Functional Reserve
Reduced Healing Capacity and Stress Resistance
Unstable Health
Failure to Thrive

Physical and Cognitive FRAILTY

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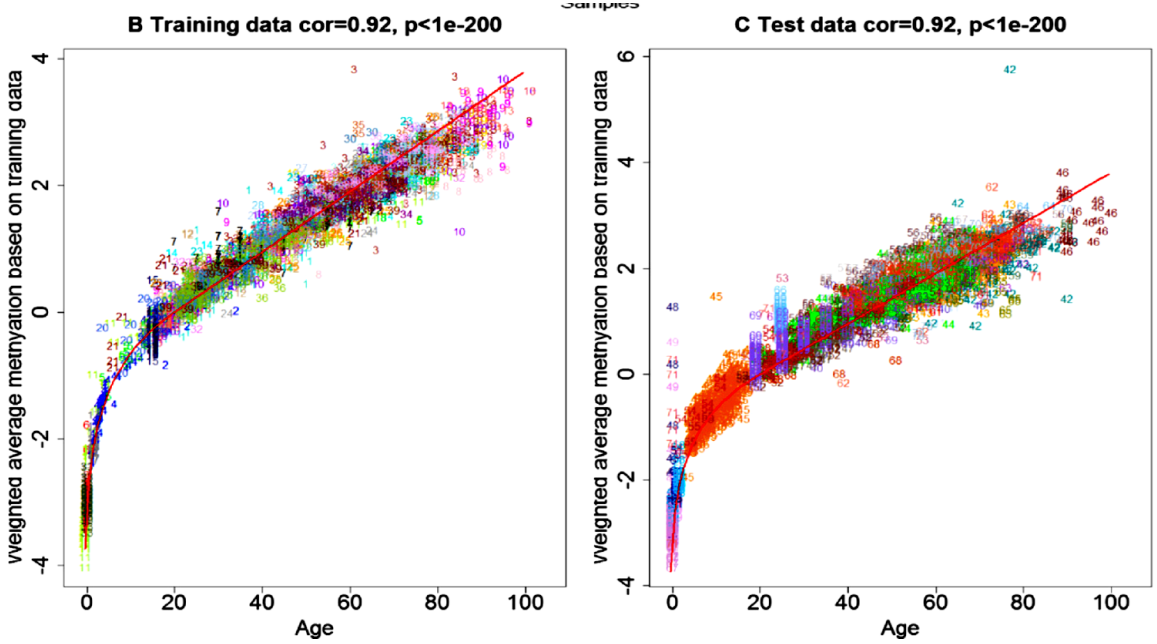
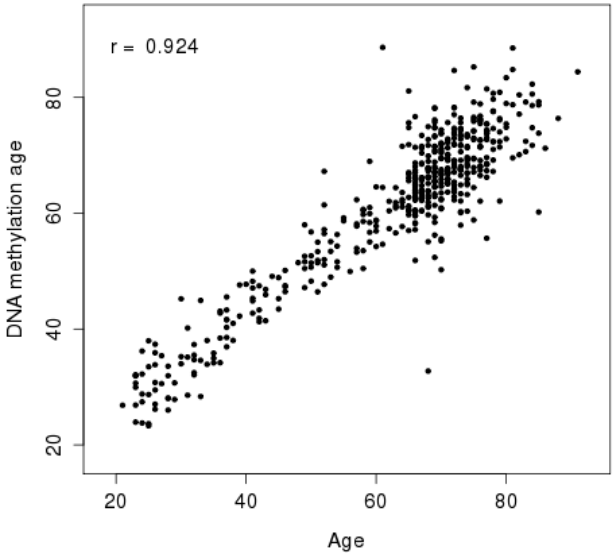
The Hallmarks of Aging
Carlos Lo´ pez-Otı´n,,Maria A. Blasco, Linda Partridge,Manuel Serrano, and Guido Kroemer. Cell 3013, 153: 1194

DNA methylation age of human tissues and cell types

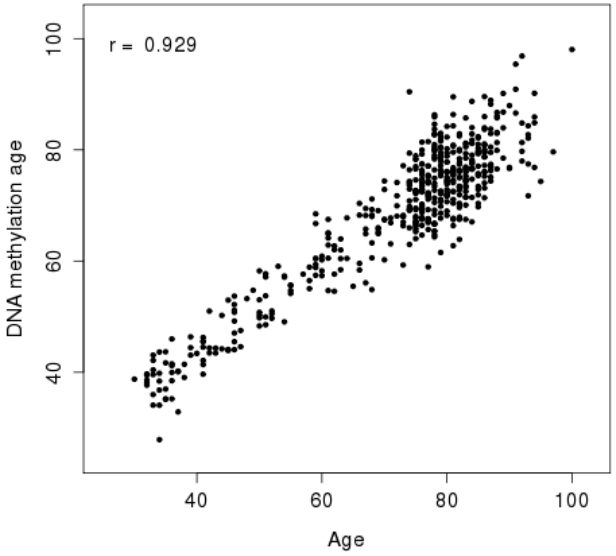
Steve Horvath at http://genomebiology.com//14/10/R115



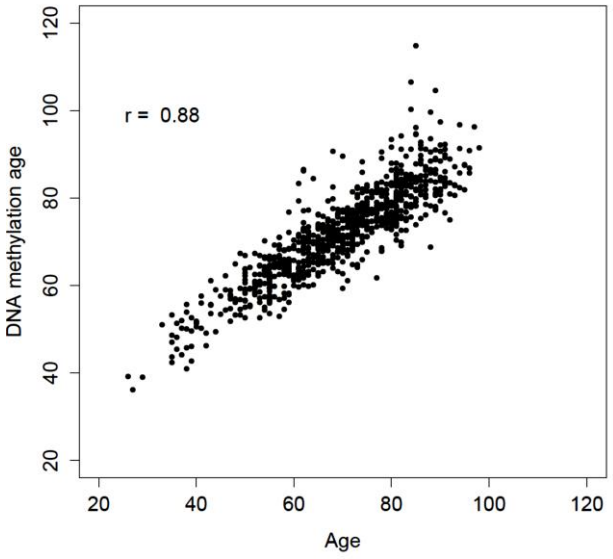
InCHIANTI Baseline (n=499)



InCHIANTI 9-year Followup (n=499)



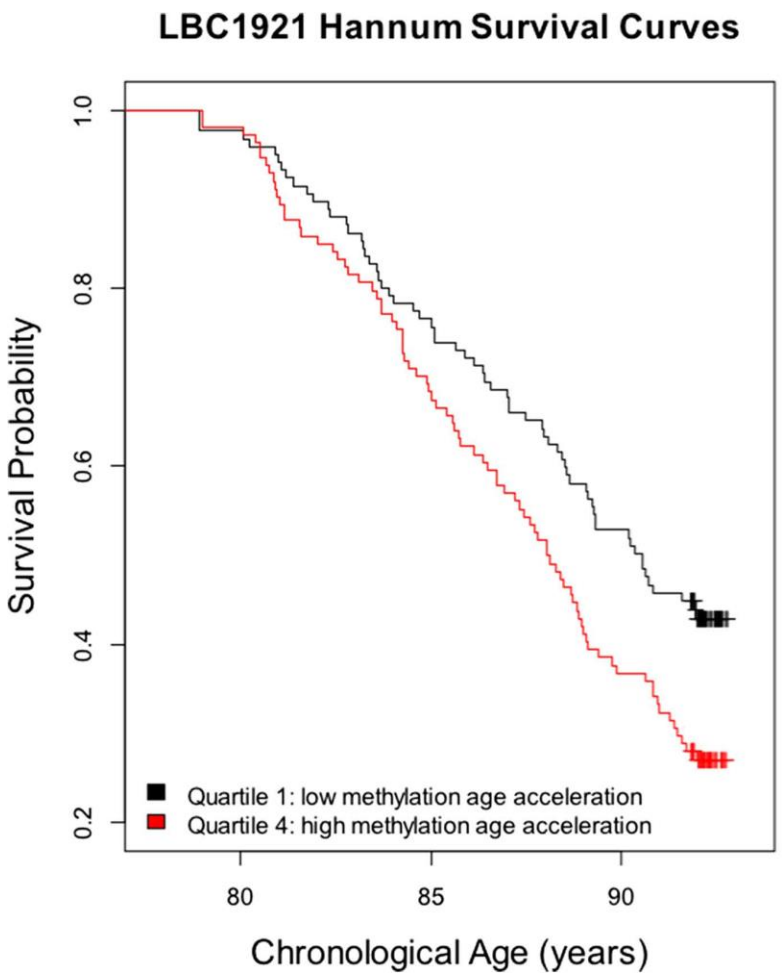
BLSA (n=1105)

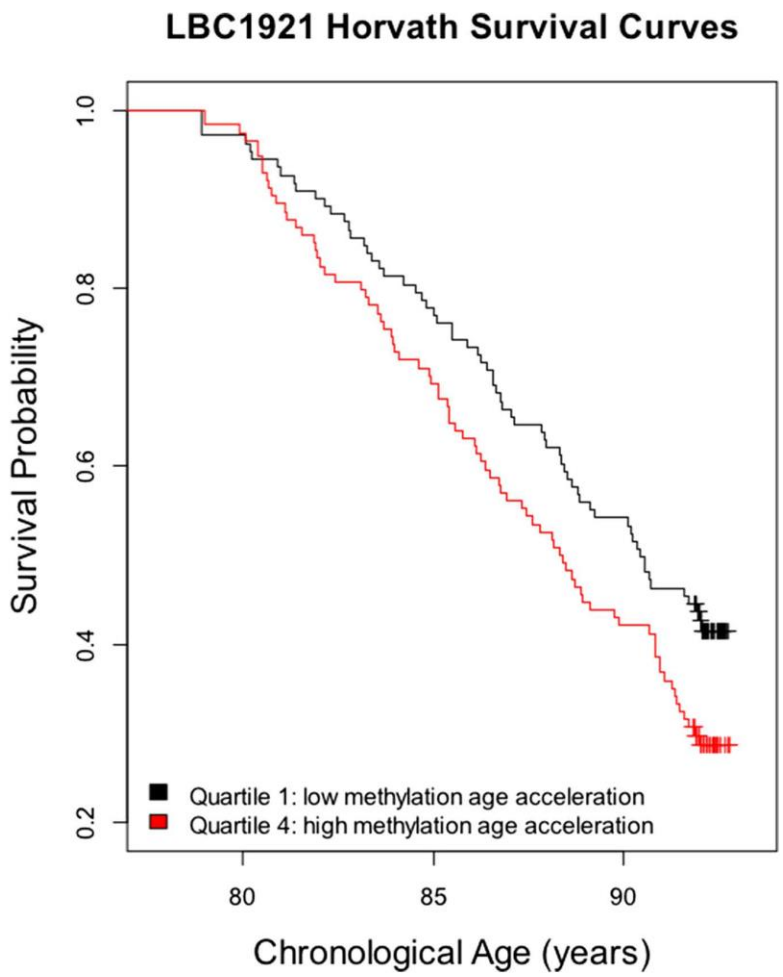


DNA methylation age of blood predicts all-cause mortality in later life

Genome Biology doi:10.1186/s13059-015-0584-6 (2015)

Riccardo E Marioni, Sonia Shah, Allan F McRae, Brian H Chen et al.





I am so lucky!!