Early cognitive changes of non-AD pathways

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- **Pearson, Inc.**

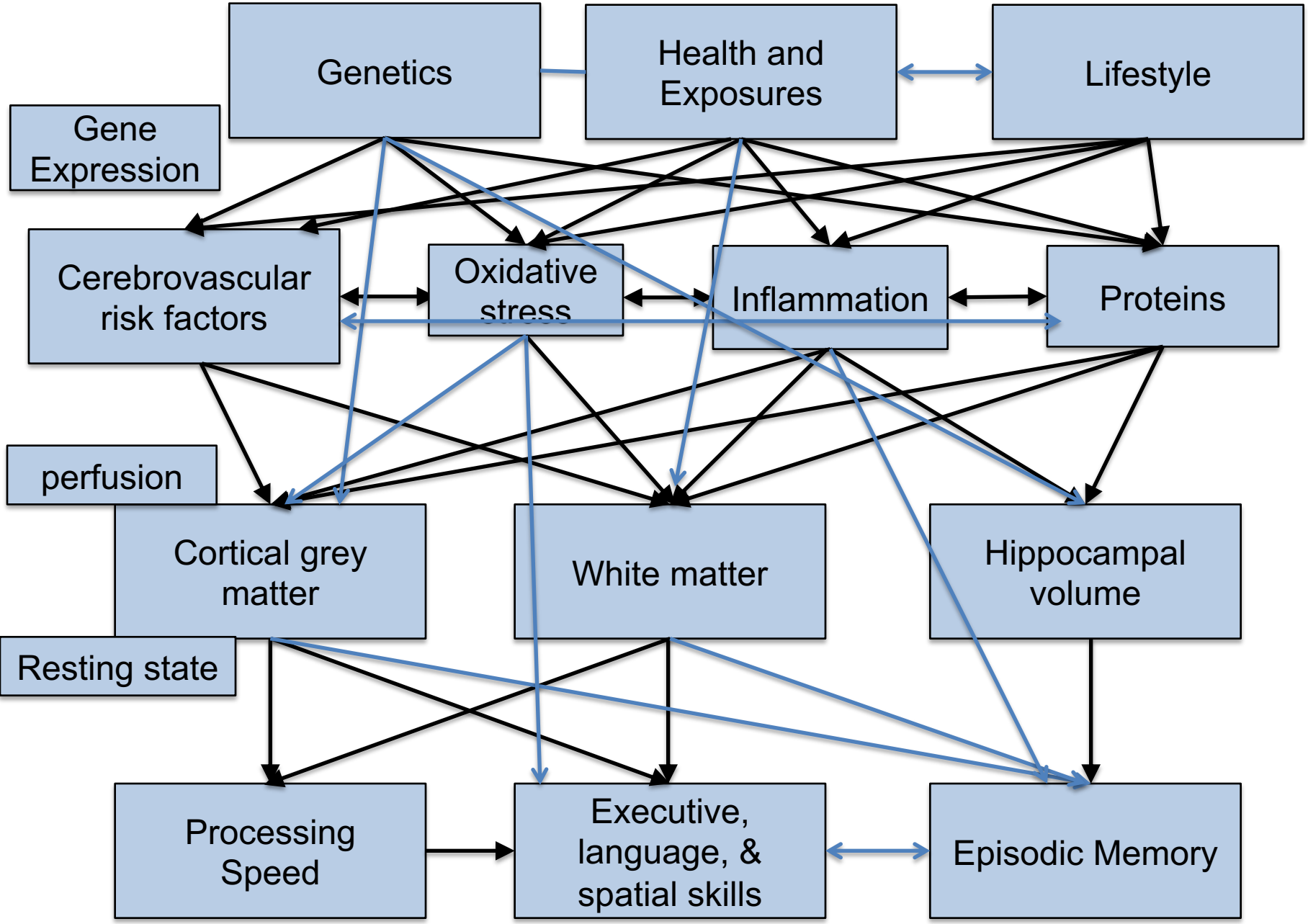
Acknowledgements

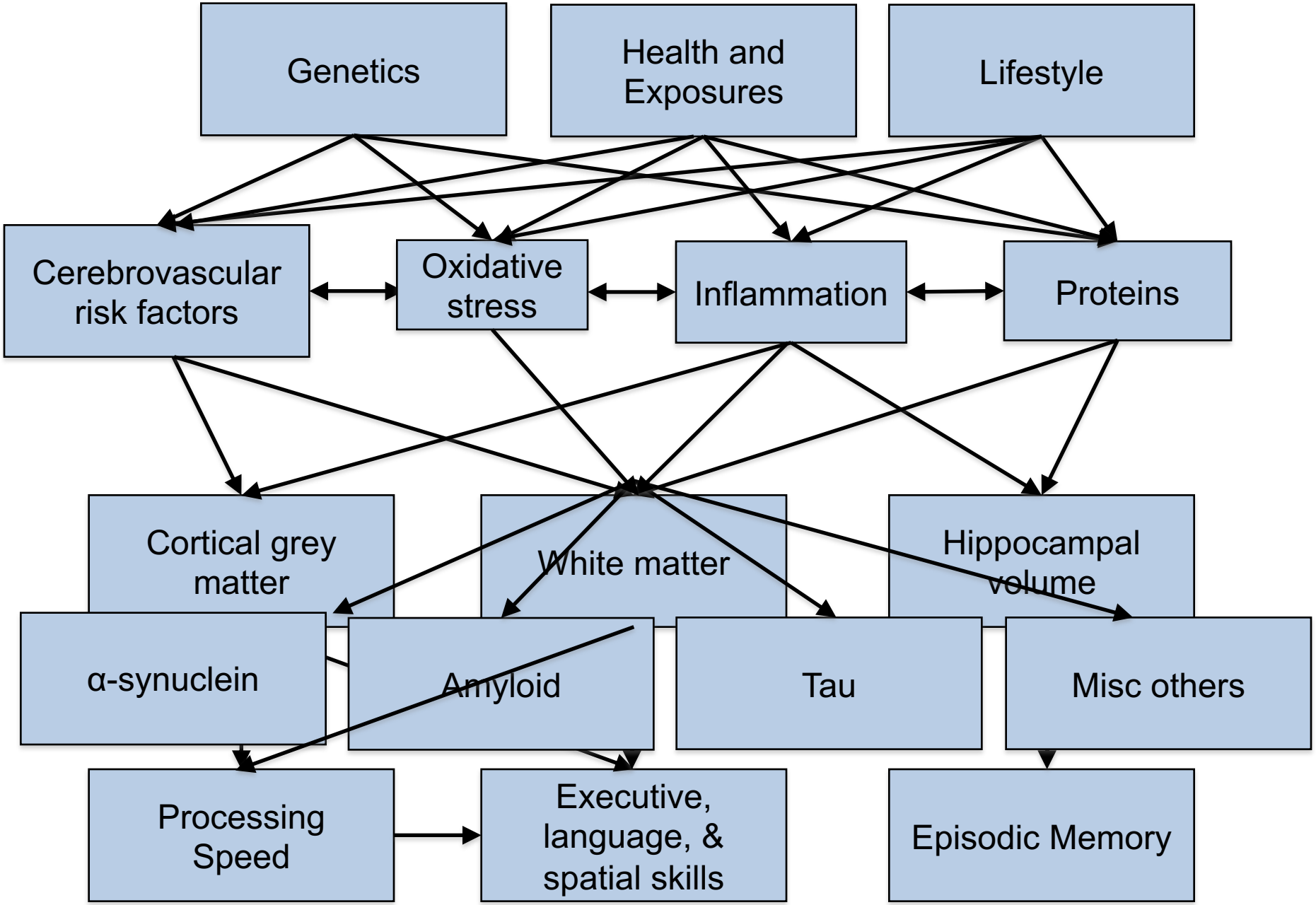
Starting point

- Decline in cognition with age and brain is not inevitable; there is considerable variability in how much and how fast
- Age-related declines in cognition and brain structure and function are the result of pathological processes
- The better we understand these processes, the better equipped we are do something about it

UCSF cohort

- **Over 635 functionally intact, community dwelling older subjects**
- **365 active in longitudinal studies**
- **Comprehensive evaluations:**
  - All with cog, neuro, med hx, CDR
  - DNA
  - Banked serum, plasma, whole blood, lymphocyes
  - MRI: structural, DTI, resting state, ASL
  - 100+ with amyloid-PET; plans for 100 tau-PET
  - 75+ with CSF


Genetics
Health and Exposures
Lifestyle
Gene Expression
Cerebrovascular risk factors
Oxidative stress
Inflammation
Proteins
perfusion
Cortical grey matter
White matter
Hippocampal volume
Resting state
Processing Speed
Executive, language, & spatial skills
Episodic Memory


Genetics
Health and Exposures
Lifestyle
Cerebrovascular risk factors
Oxidative stress
Inflammation
Proteins
Cortical grey matter
White matter
Hippocampal volume
α-synuclein
Amyloid
Tau
Misc others
Processing Speed
Executive, language, & spatial skills
Episodic Memory

Klotho

- **KLOTHO (KL)**
  - Transmembrane protein throughout body and brain
  - AMPA and NMDA receptors; insulin response
- ***KLOTHO* (*KL*): F352V and C370S ("KL-VS")**
  - 20-25% heterozygosity
  - 1.6x increase in protein levels
  - Longevity; protection against age-related disease
  - Cognitive enhancement in aging humans

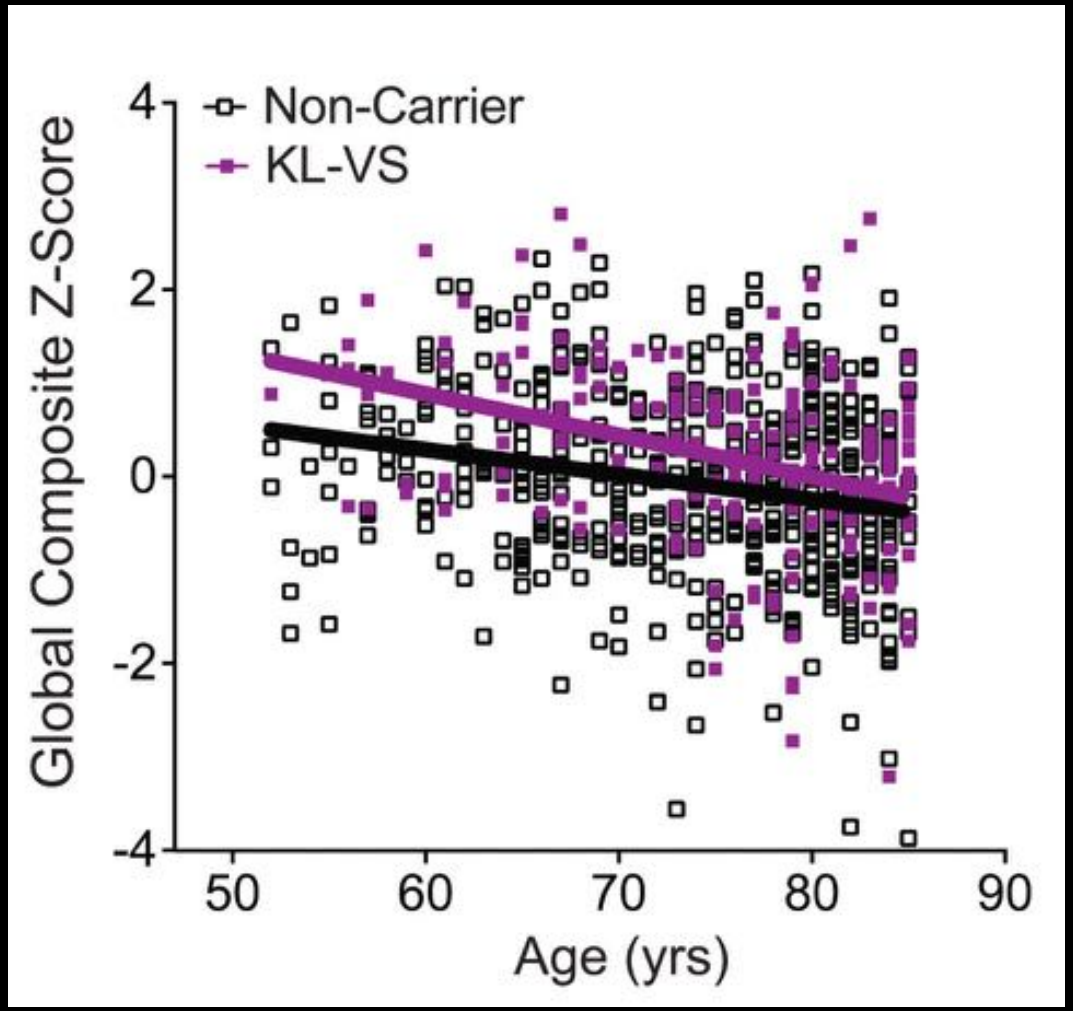
Protective KL-VS genotype

- Greater volume in a relevant brain region

- Carrying 1 copy of KL-VS is associated with greater volume in right DLPFC

Protective KL-VS genotype

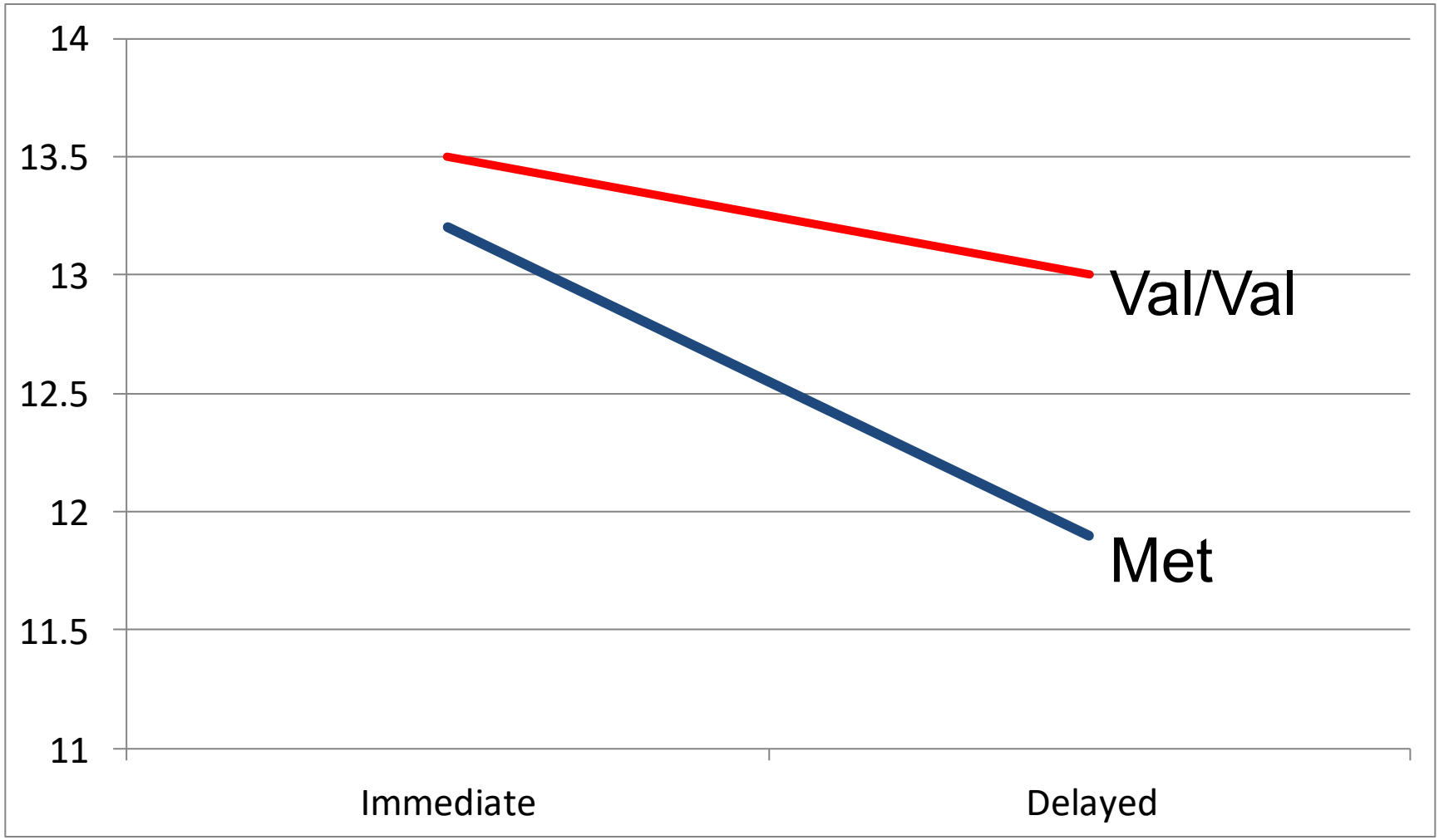
- Carrying 1 copy of KL-VS is associated with better <u>executive function</u> in two healthy aging cohorts



Brain derived neurotrophic factor (BDNF)

- **Neurotrophic factors support the health and functioning of neurons**
- **Heavily expressed in hippocampus and cortex**
- **Involved in neurogenesis**
- **Normal genetic variability (methionine versus valine in codon 66) influences activity-dependent secretion**
  - 65% are Val/Val; 30% Val/Met; 5% Met/Met
  - Met allele increases risk of cognitive and psychiatric problems; lower hippocampal activation on memory tasks during fMRI

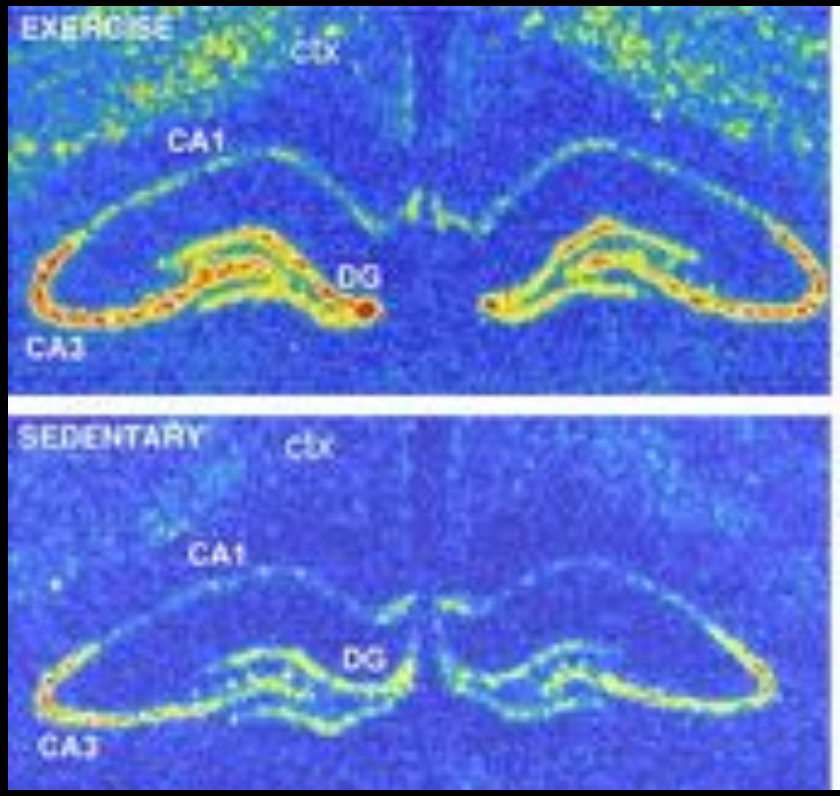
BDNF and verbal memory

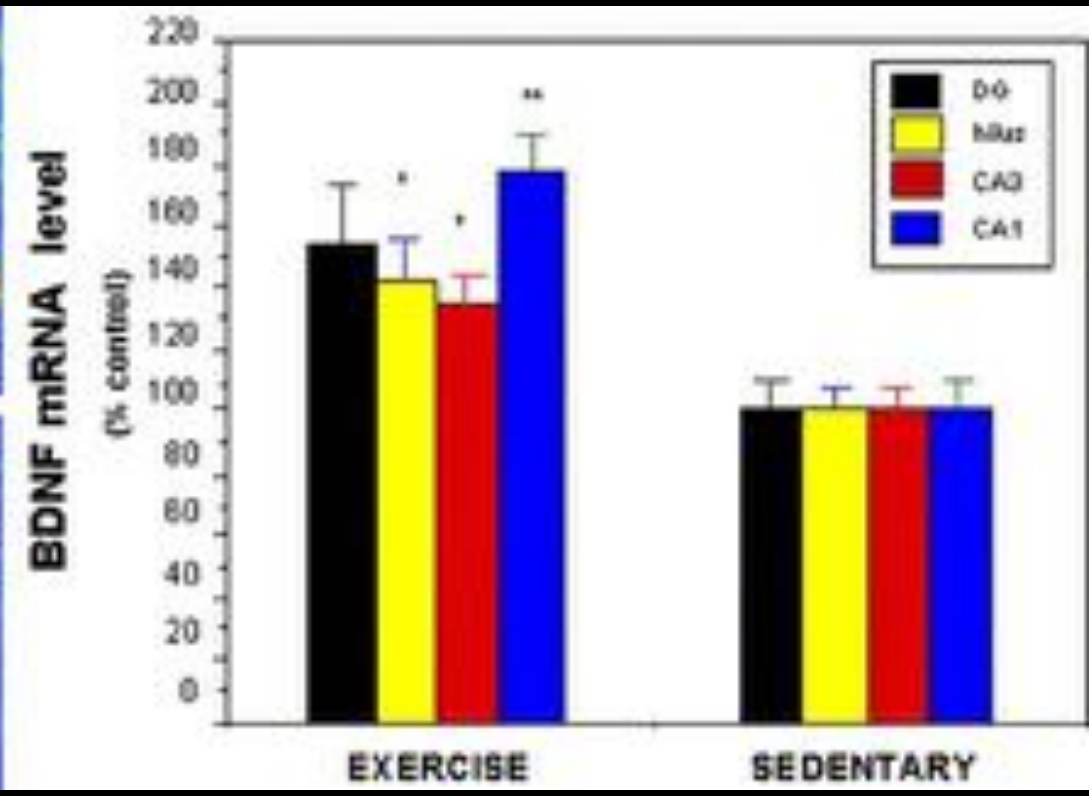


Carl Cotman and colleagues

Physical Exercise and BDNF

Voluntary running in rats associated with 20% increase in BDNF mRNA





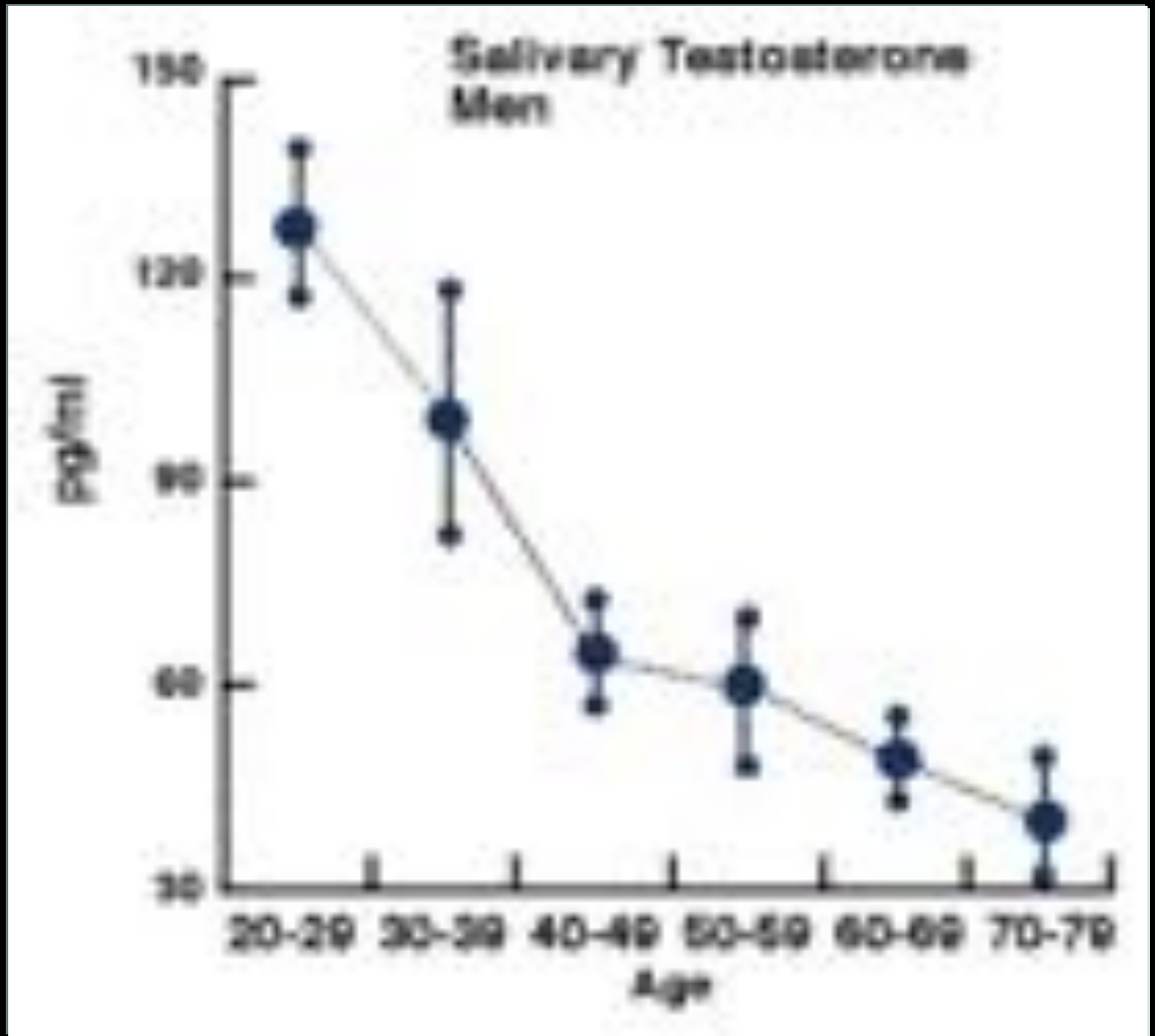
Improvements in function?

- Exercise is associated with improved memory performance in older rats
- If exercise is begun early in life, mice genetically predisposed to developing AD have fewer cognitive deficits
- Older transgenic mice exposed to 3 weeks of running improved memory performance, whereas sedentary transgenic mice showed a decline

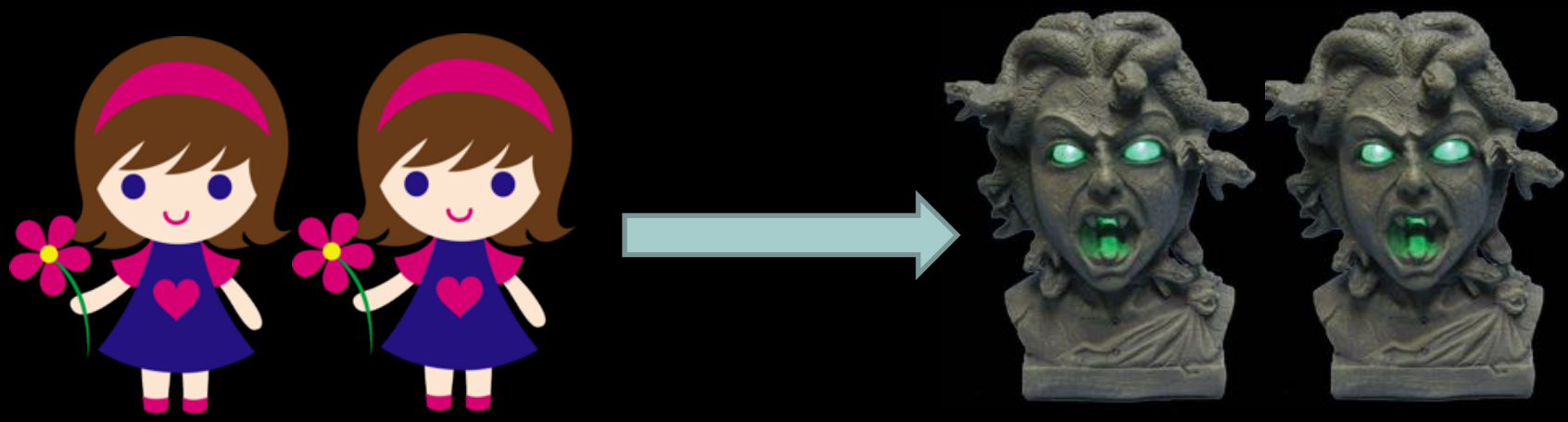
Physical exercise: Trial

- **Art Kramer lab**
- **Randomized study with 120 older adults**
- **One-year trial of aerobic exercise vs stretching**
- **Aerobic exercise led to increase in size of anterior hippocampus and better spatial memory**
  - Associated with serum levels of BDNF

Testosterone



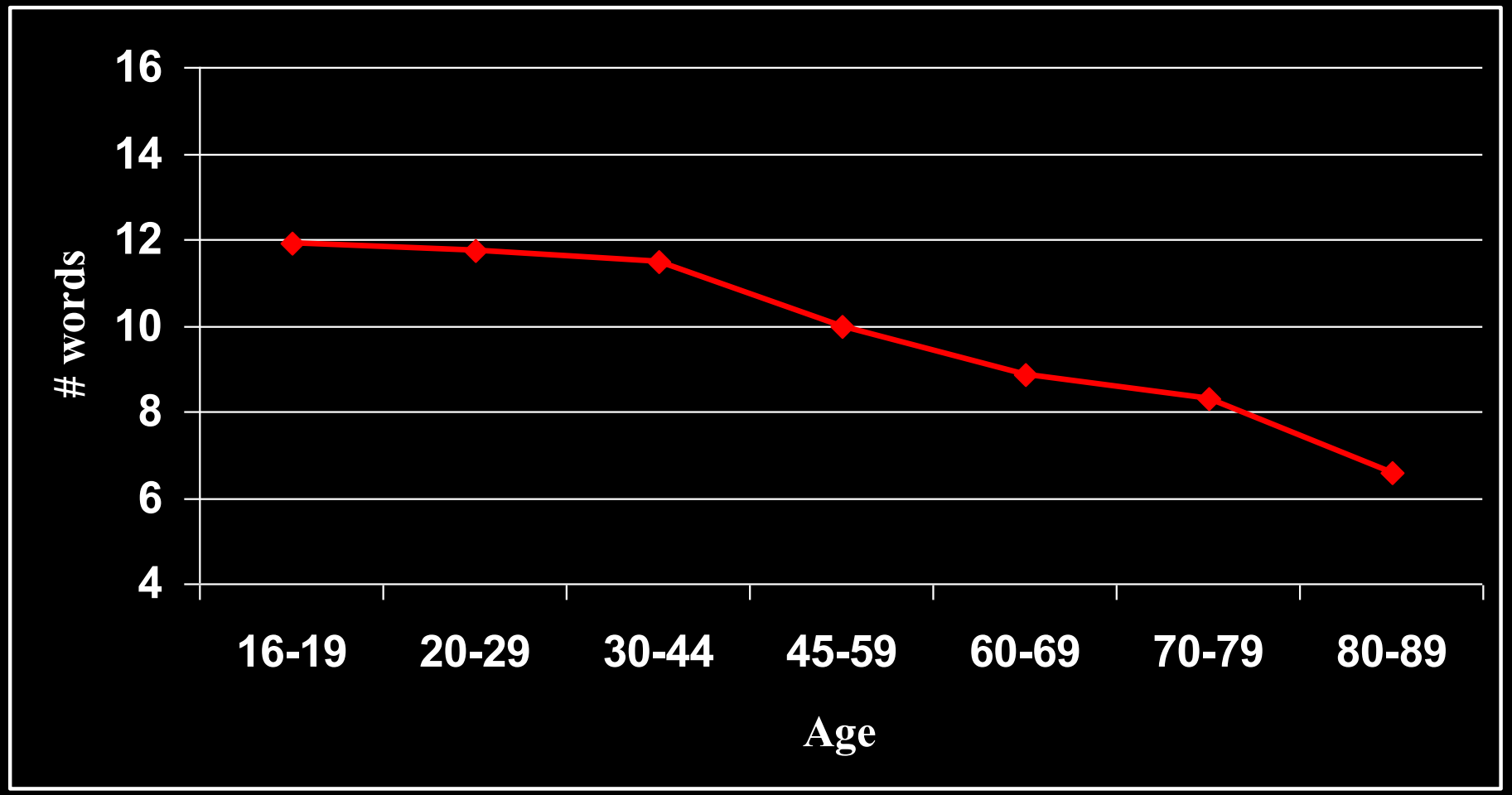
Estrogen



Estrogen & neuroprotection

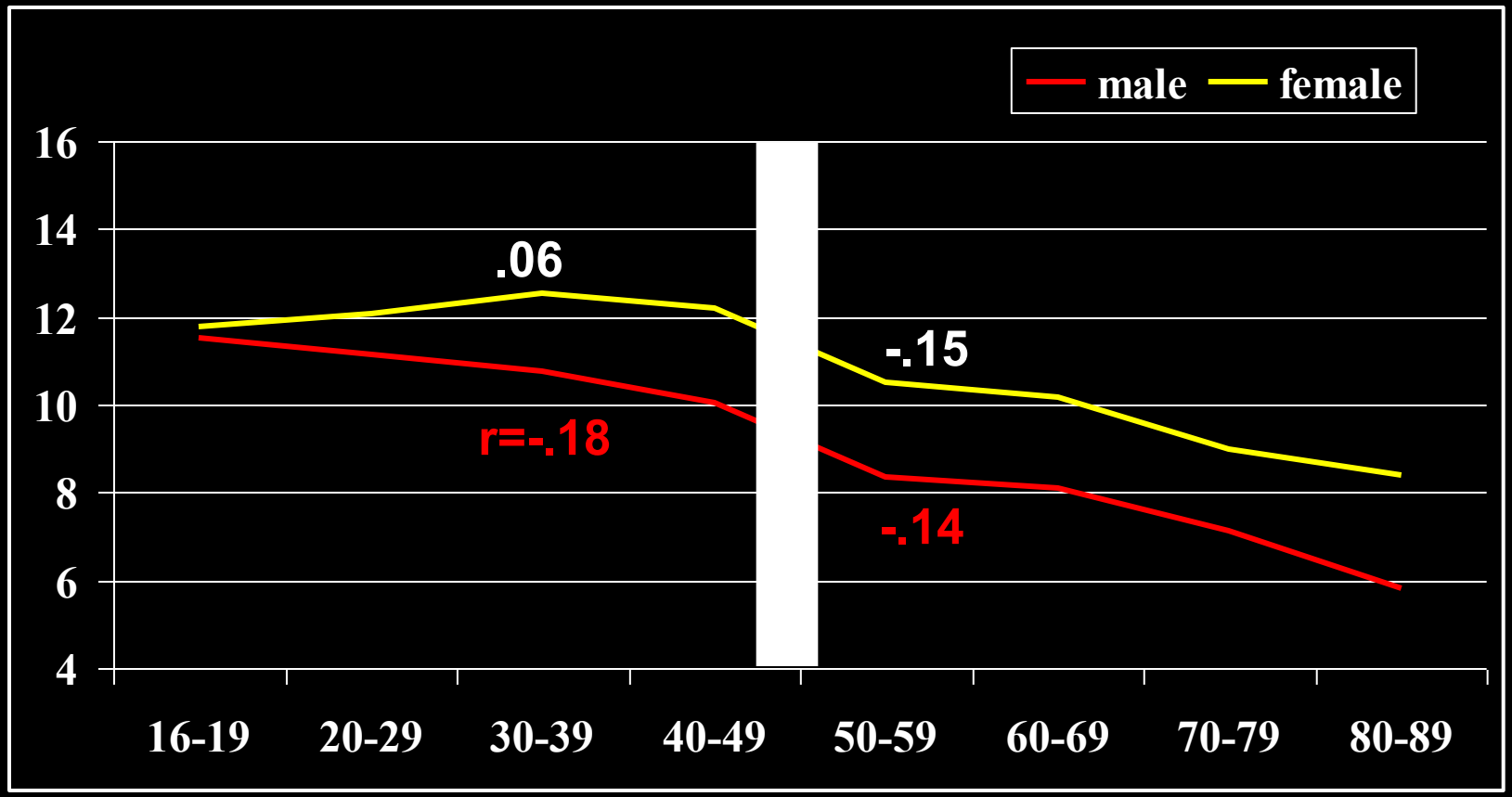
- **Female rodents and pre-menopausal women are more resilient to stroke and ischemia.**
- **Specific protective role in the CA1 region of the hippocampus**
  - Correlation with dentritic spine and synaptic density
- **Significantly lower levels of reactive oxygen species following neuronal injury**
- **Impact on human condition**
  - Verbal working memory and midluteal stage
  - Verbal memory and HRT

Delayed Free Recall

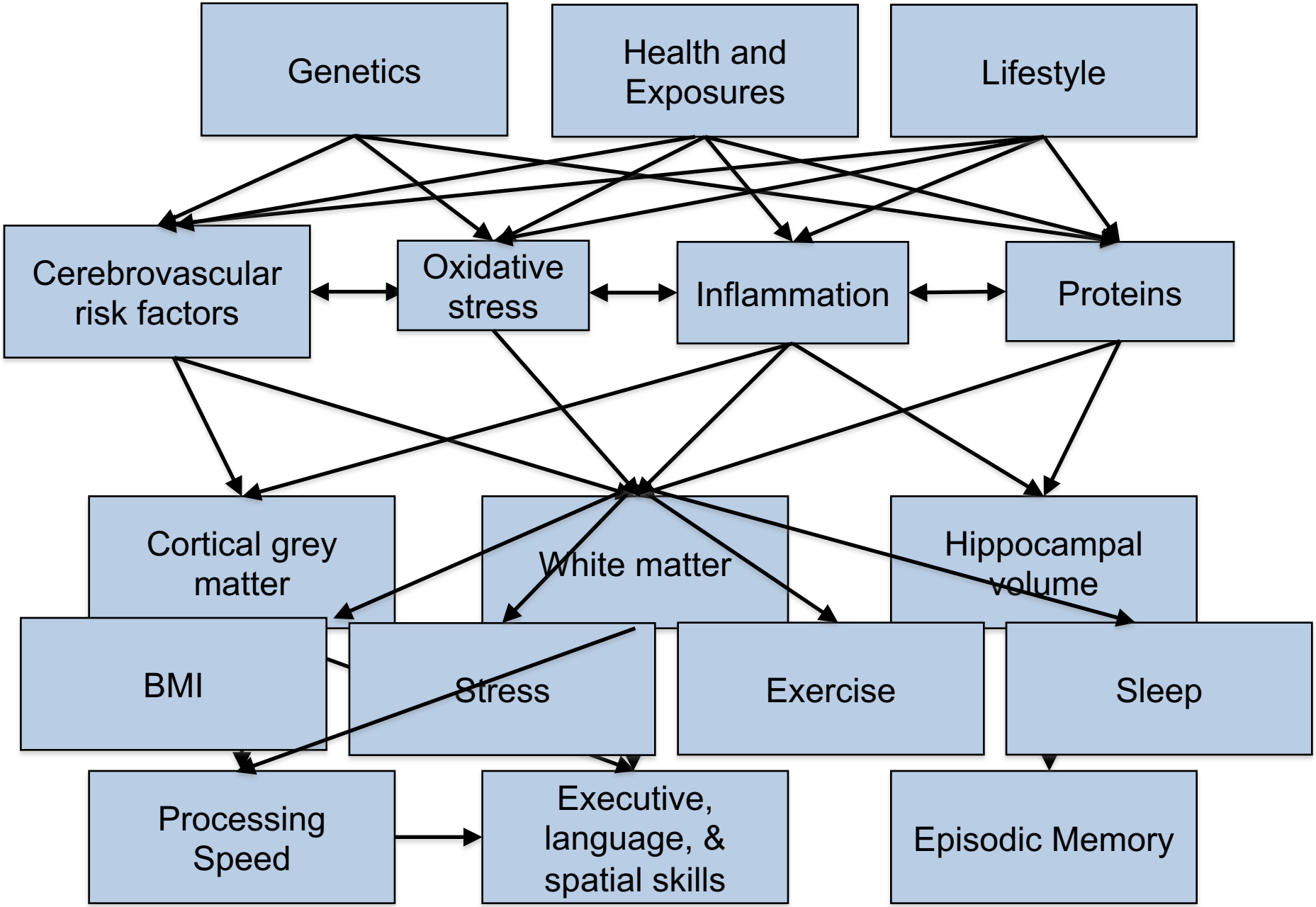


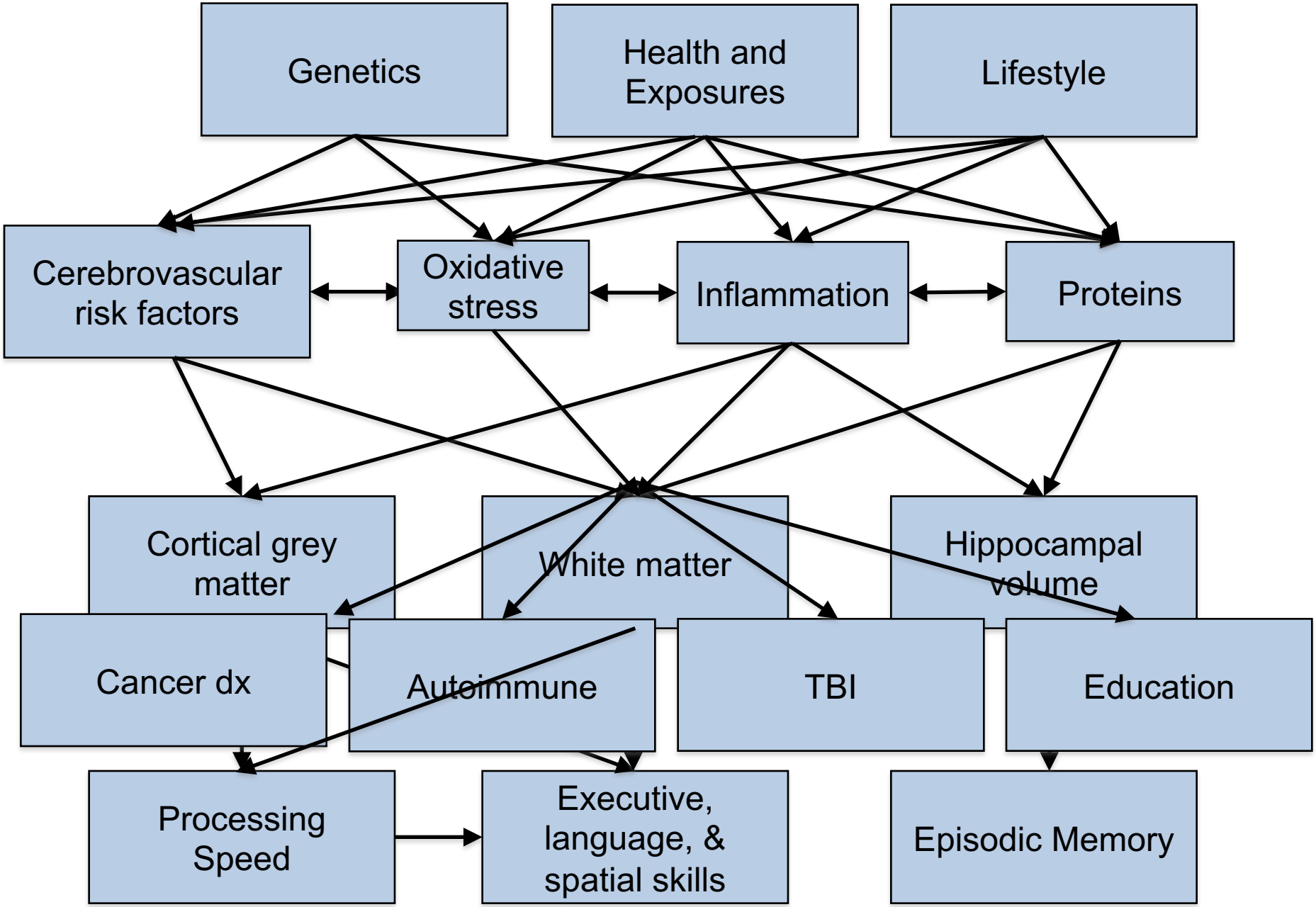
Kramer et al., 2004

Delayed Free Recall



Kramer et al., 2004


Genetics
Health and Exposures
Lifestyle
Cerebrovascular risk factors
Oxidative stress
Inflammation
Proteins
Cortical grey matter
White matter
Hippocampal volume
BMI
Stress
Exercise
Sleep
Processing Speed
Executive, language, & spatial skills
Episodic Memory

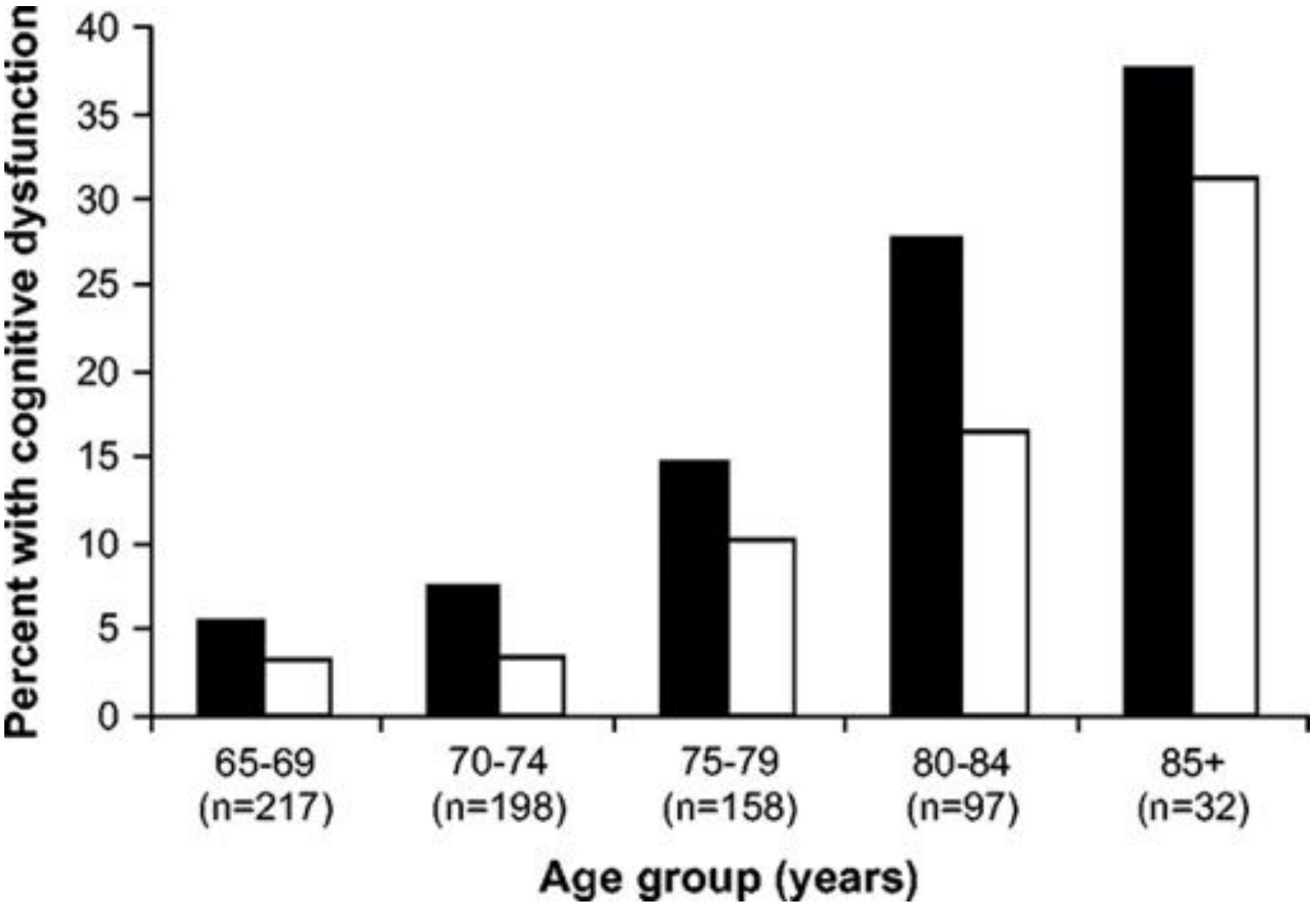

Genetics
Health and Exposures
Lifestyle
Cerebrovascular risk factors
Oxidative stress
Inflammation
Proteins
Cortical grey matter
White matter
Hippocampal volume
Cancer dx
Autoimmune
TBI
Education
Processing Speed
Executive, language, & spatial skills
Episodic Memory

Impact of a cancer dx

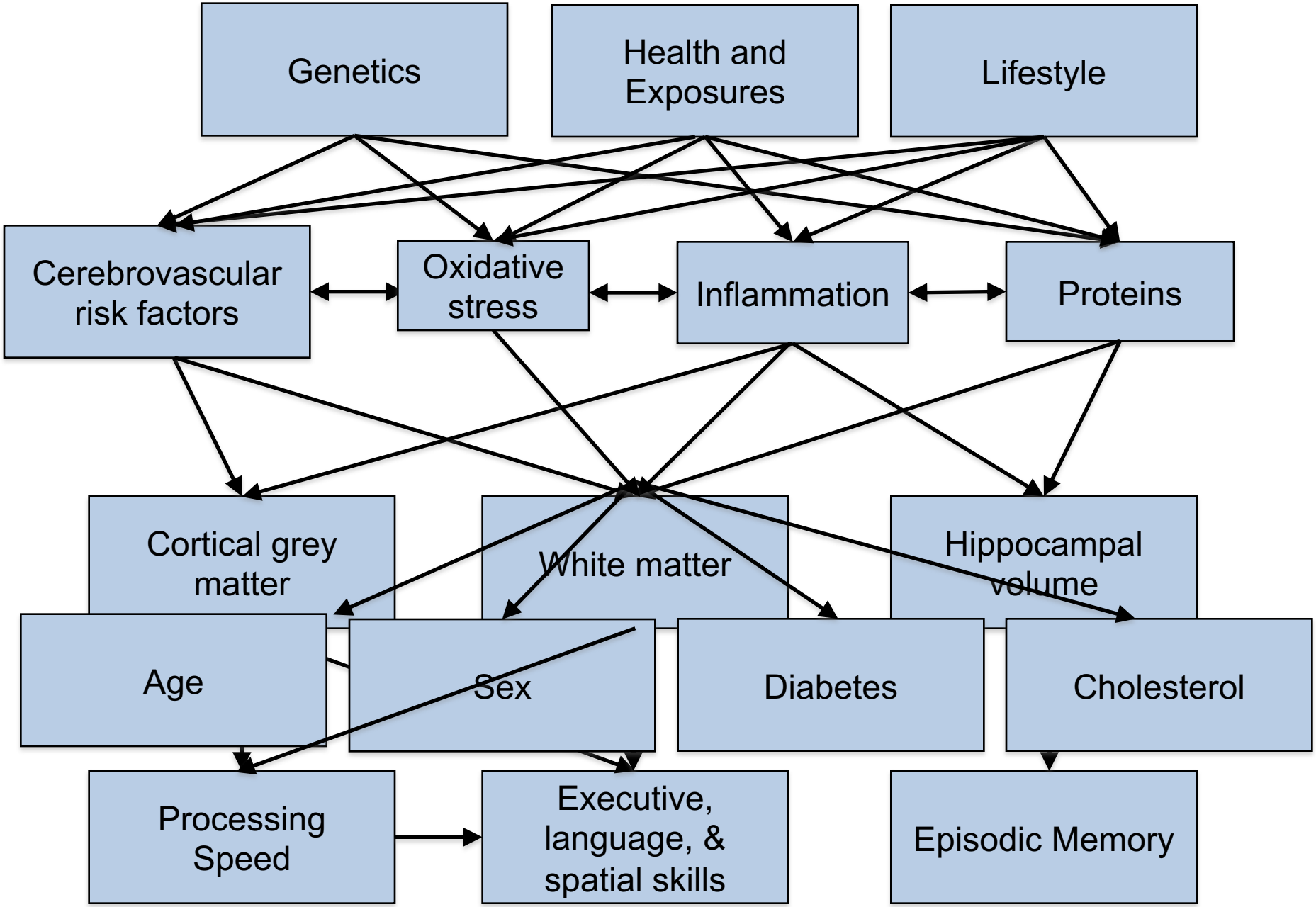
- Retrospective study
- Swedish Twin Registry & Swedish Cancer Registry
- Aged ≥ 65 years
- Co-twin control design
- N=486 twin pairs

  discordant for cancer

Percentage of cancer-surviving and cancer-free twins classified by cognitive screening as having cognitive dysfunction.



Lara H. Heflin et al. JNCI J Natl Cancer Inst 2005;97:854-856


Genetics
Health and Exposures
Lifestyle
Cerebrovascular risk factors
Oxidative stress
Inflammation
Proteins
Cortical grey matter
White matter
Hippocampal volume
Age
Sex
Diabetes
Cholesterol
Processing Speed
Executive, language, & spatial skills
Episodic Memory

Predicting executive functioning: Insulin resistance

	β	p-value
Age	-.31	.00
Education	.12	.19
Gender	-.11	.20
LDL	.12	.18
BMI	.11	.34
MAP	-.07	.45
WMH	-.24	.02
HOMA-IR	-.25	.02

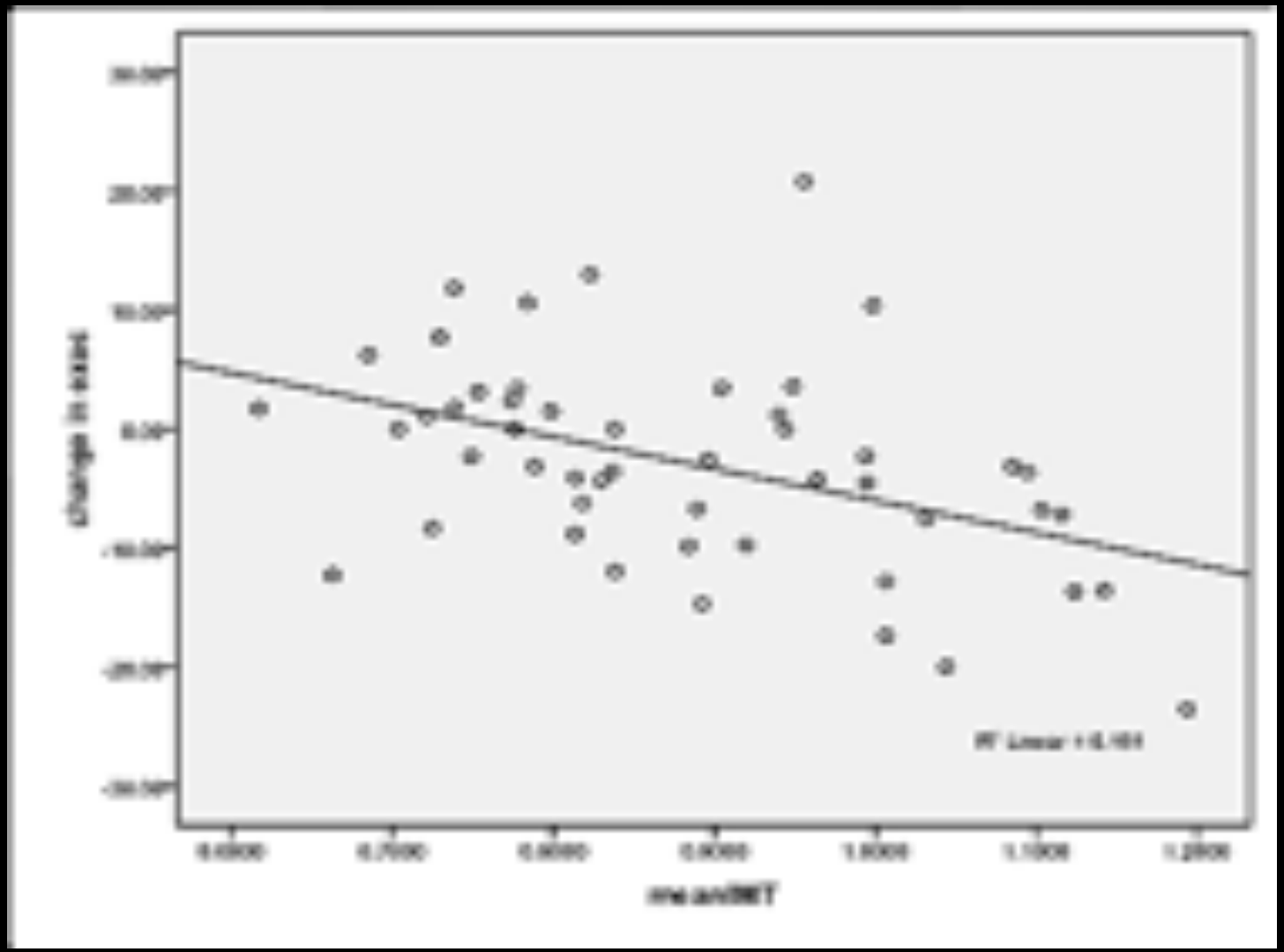
Frazier et al., 2015

Predicting executive functioning: Triglycerides

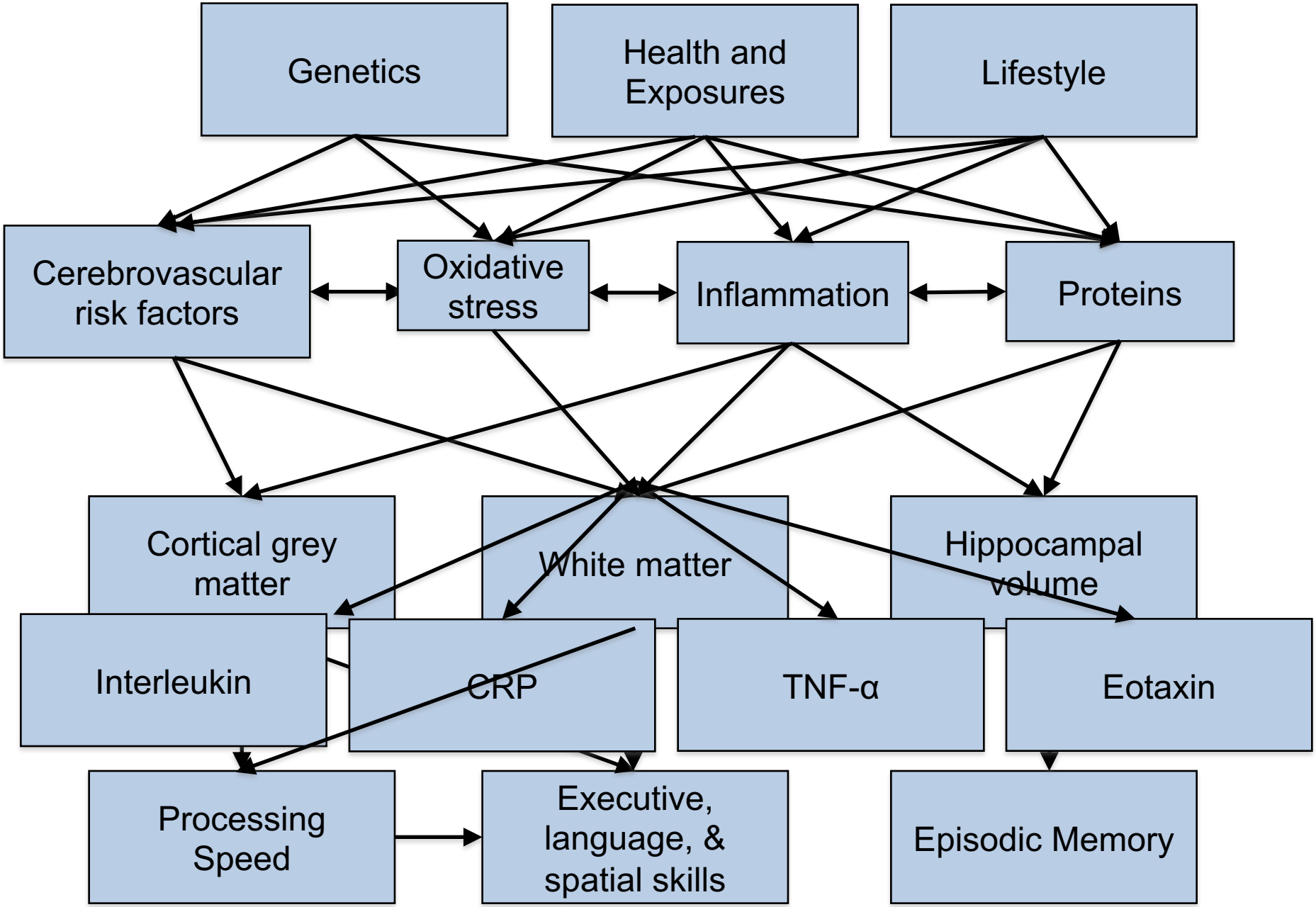
	β	p-value
Age	-0.16	0.04
Education	0.24	0.00
Gender	0.10	0.16
LDL	-0.03	0.36
ApoE4 Status	-0.62	0.54
CDR	-0.30	0.00
Global FA	-0.03	0.71
Triglycerides	**-0.20**	**0.01**

Parthasarathy, under review

Atherosclerosis and change in EF



Frazier et al., 2014

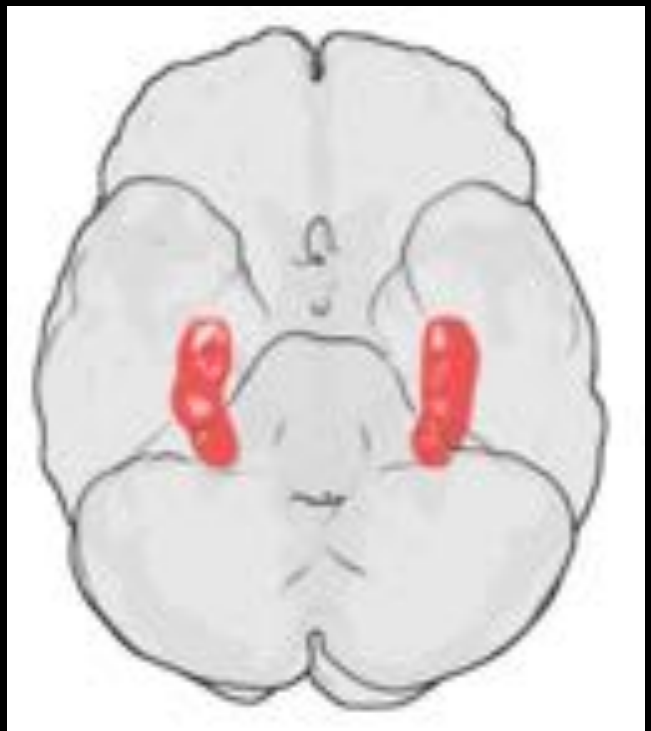

Genetics
Health and Exposures
Lifestyle
Cerebrovascular risk factors
Oxidative stress
Inflammation
Proteins
Cortical grey matter
White matter
Hippocampal volume
Interleukin
CRP
TNF-α
Eotaxin
Processing Speed
Executive, language, & spatial skills
Episodic Memory

The neuroinflammation story

- Inflammation is a normal response to injury
- Peripheral injury rapidly leads to an inflammatory response in the brain
- This inflammatory response is adaptive as long as the inflammation subsides

Aging and Immunosenescence

- In older animals, neuroinflammation persists much longer than in younger animals
- Sustained inflammation evident in the hippocampus, and is associated with problems with LTP and memory formation (S. Maier)

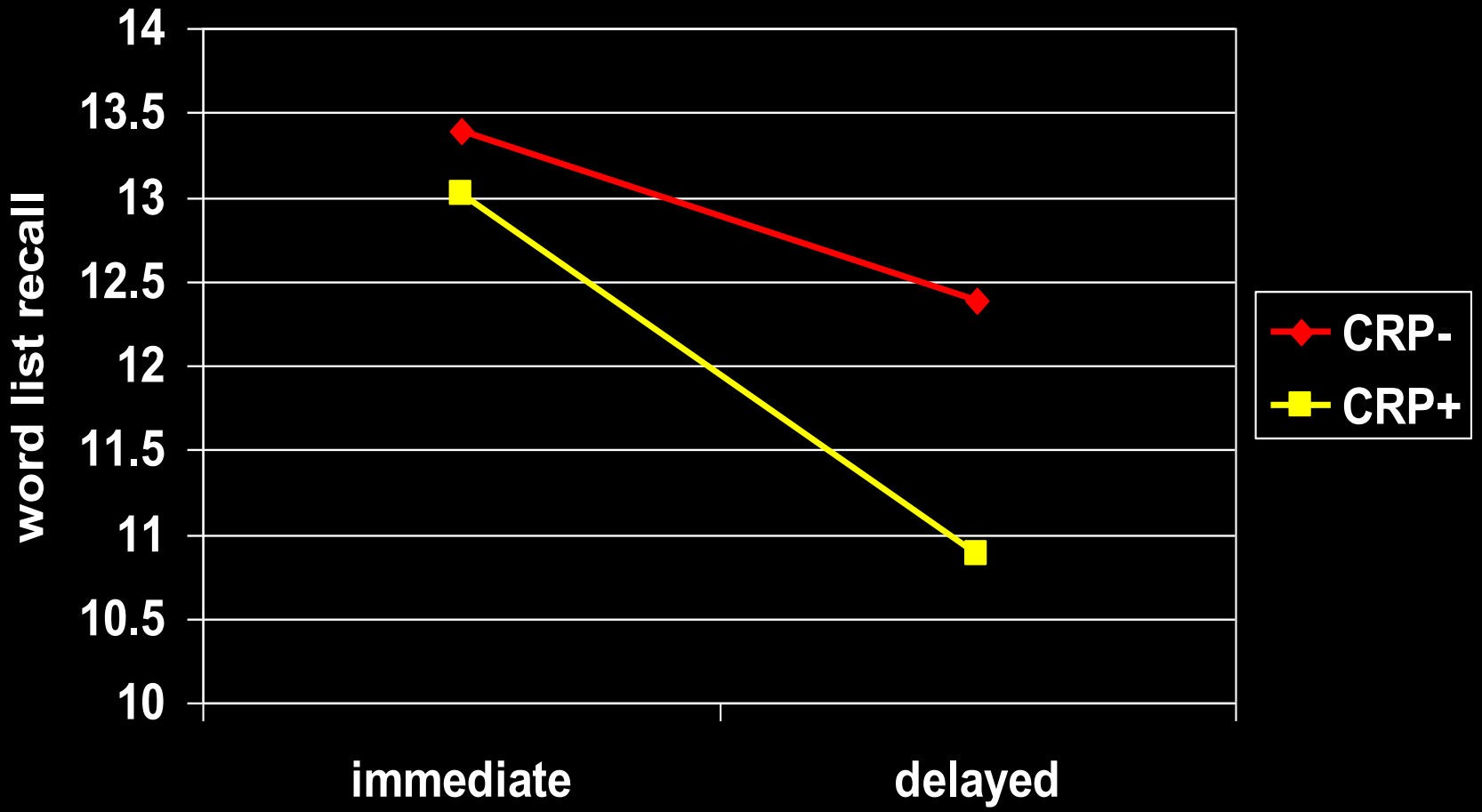


C-reactive protein

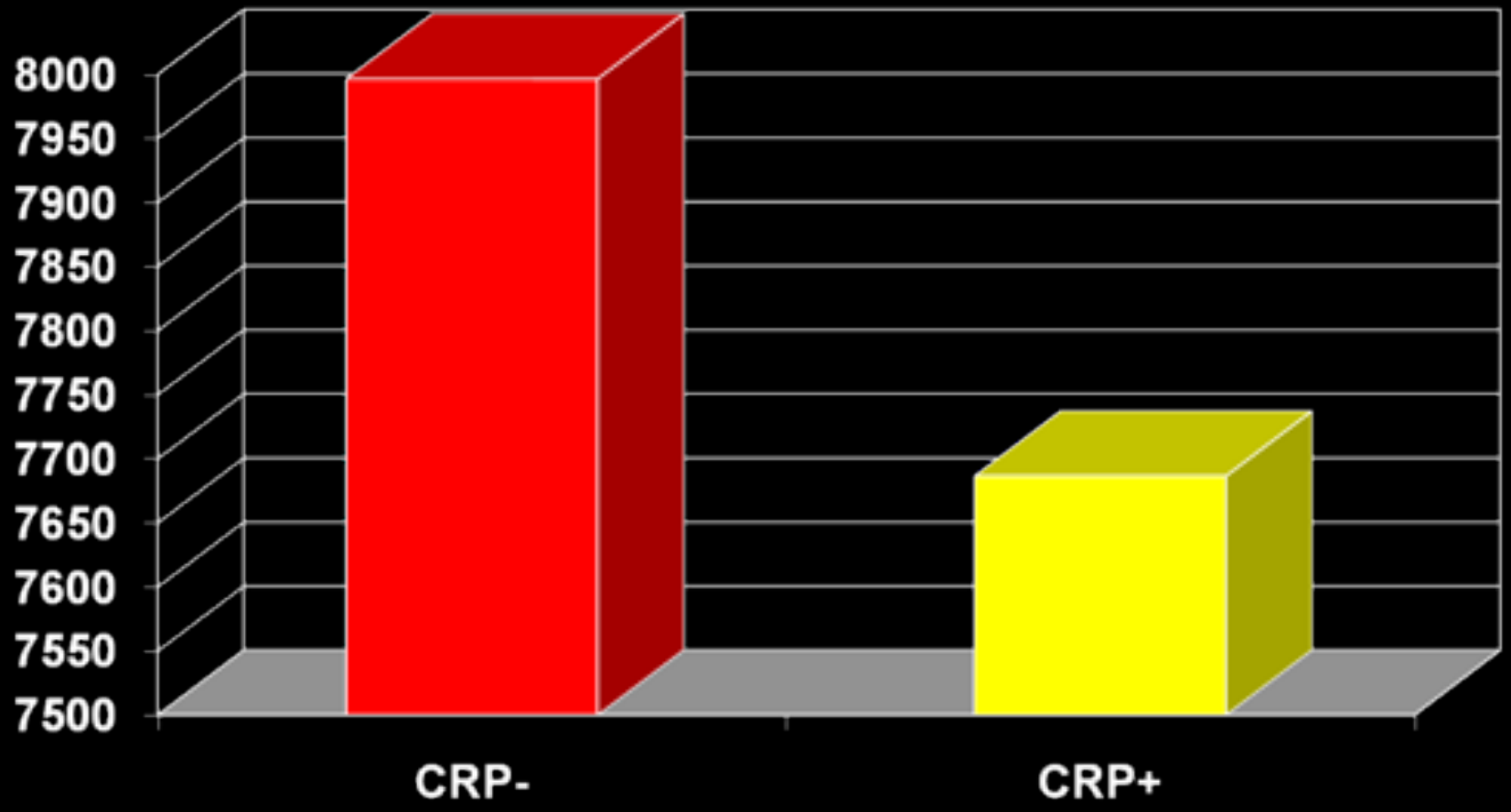
- C-reactive protein (CRP) **is a protein found in the blood, the levels of which rise in response to inflammation**
- **Elevated in AD; may lead to increase β-amyloid**
- **We measured CRP in 141 subjects, 76 of whom had detectible levels in the blood, and 65 of whom did not, and looked at their memory performance**
- **We were particularly interested in how well they held on to information over delays**

Bettcher et al., 2011

C-reactive protein and memory consolidation



CRP & medial temporal volumes

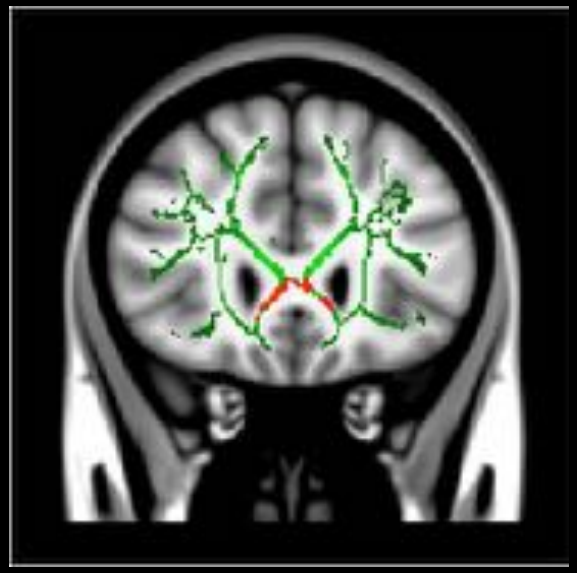


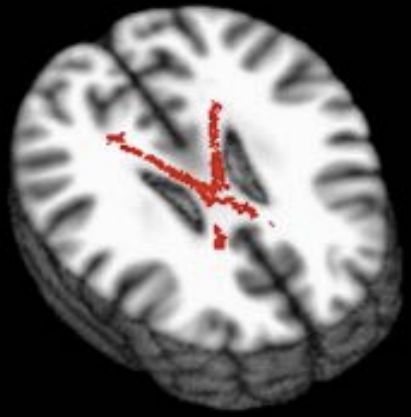
Inflammation and white matter

- Looked at CRP, TNF-α, and IL-6

- Detectable levels of inflammatory markers were related to lower white matter integrity

- This relationship is more pronounced with age

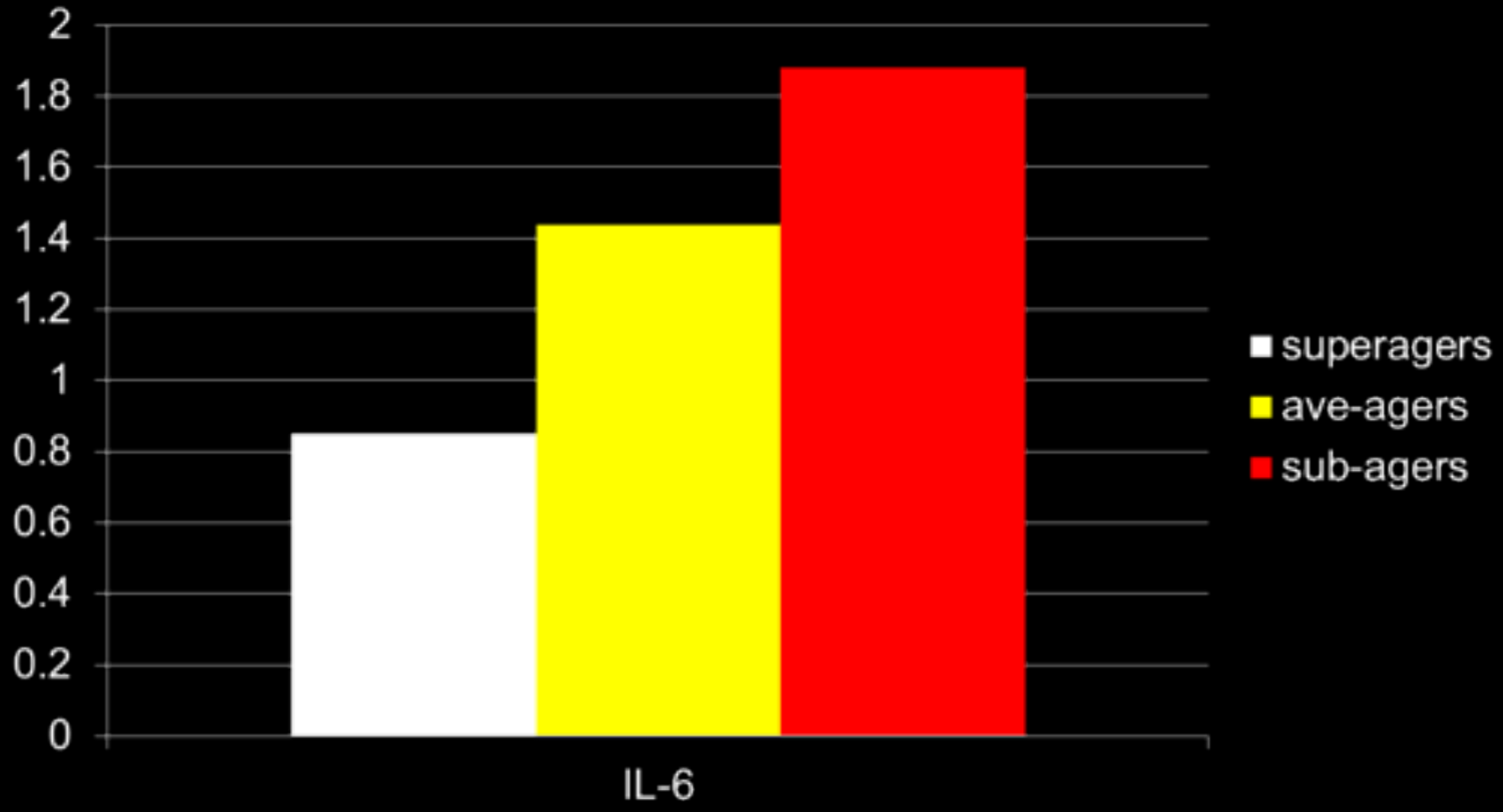




IL-6 and longitudinal change

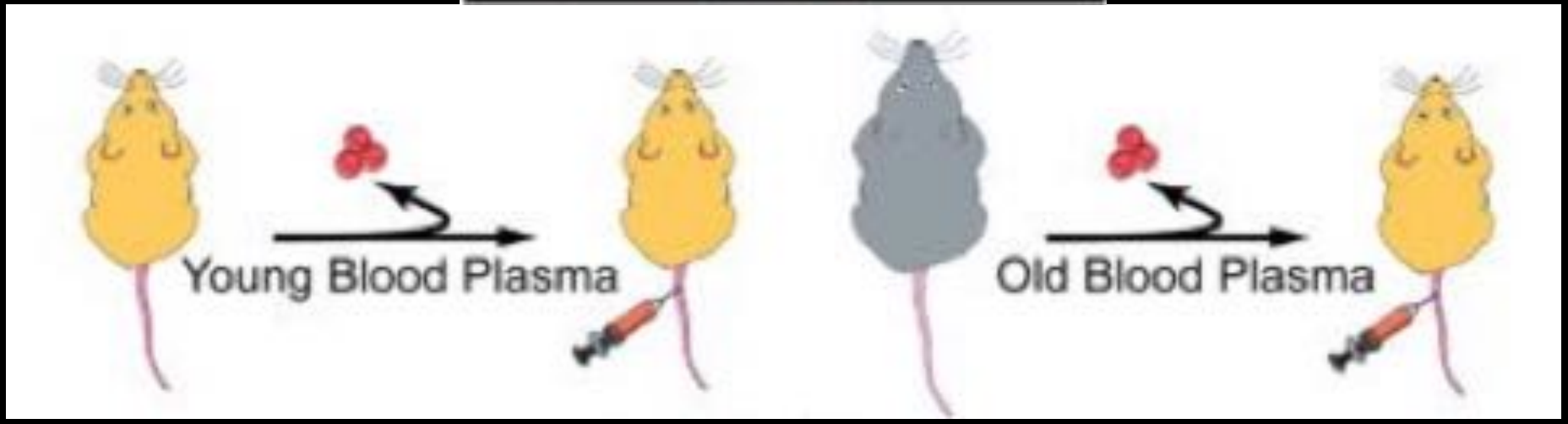
- **Higher peripheral IL-6 levels predicted greater cognitive slowing across two time points after adjusting for age, baseline processing speed, vascular risk factors, and cerebrovascular disease.**

Lower IL-6 in super-agers



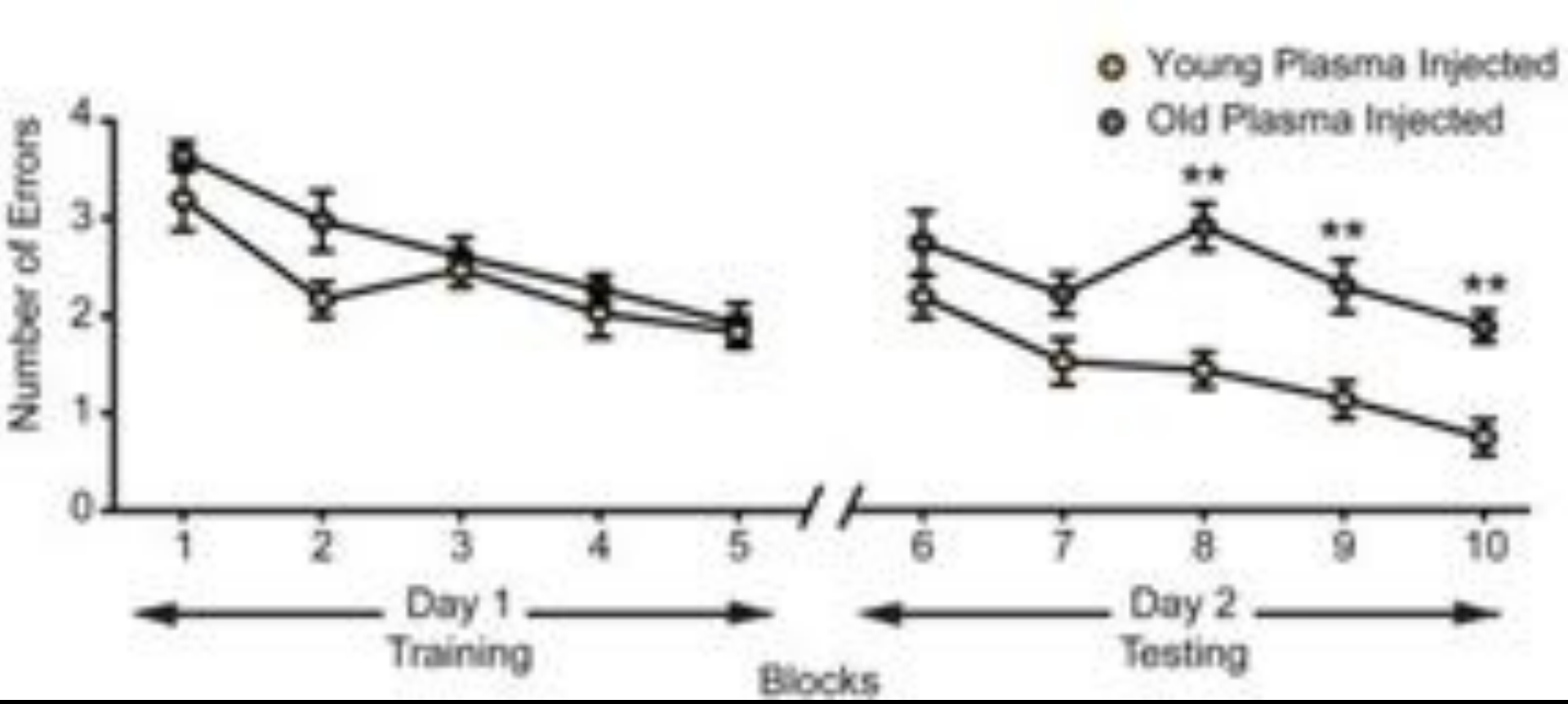
Bott et al., in prep

Age-related changes in plasma (Eotaxin-1)



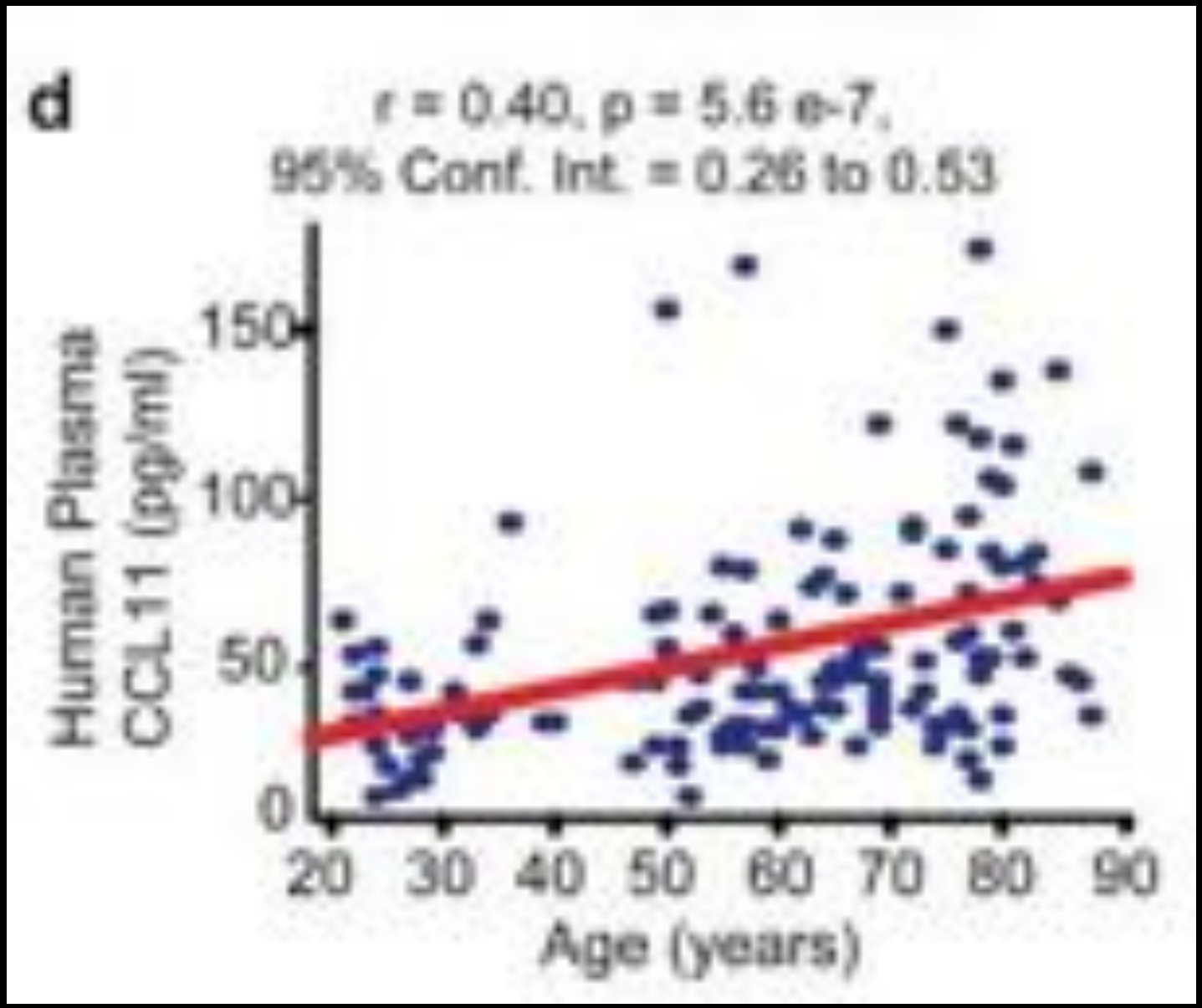
Villeda et al., 2011

Eotaxin and memory

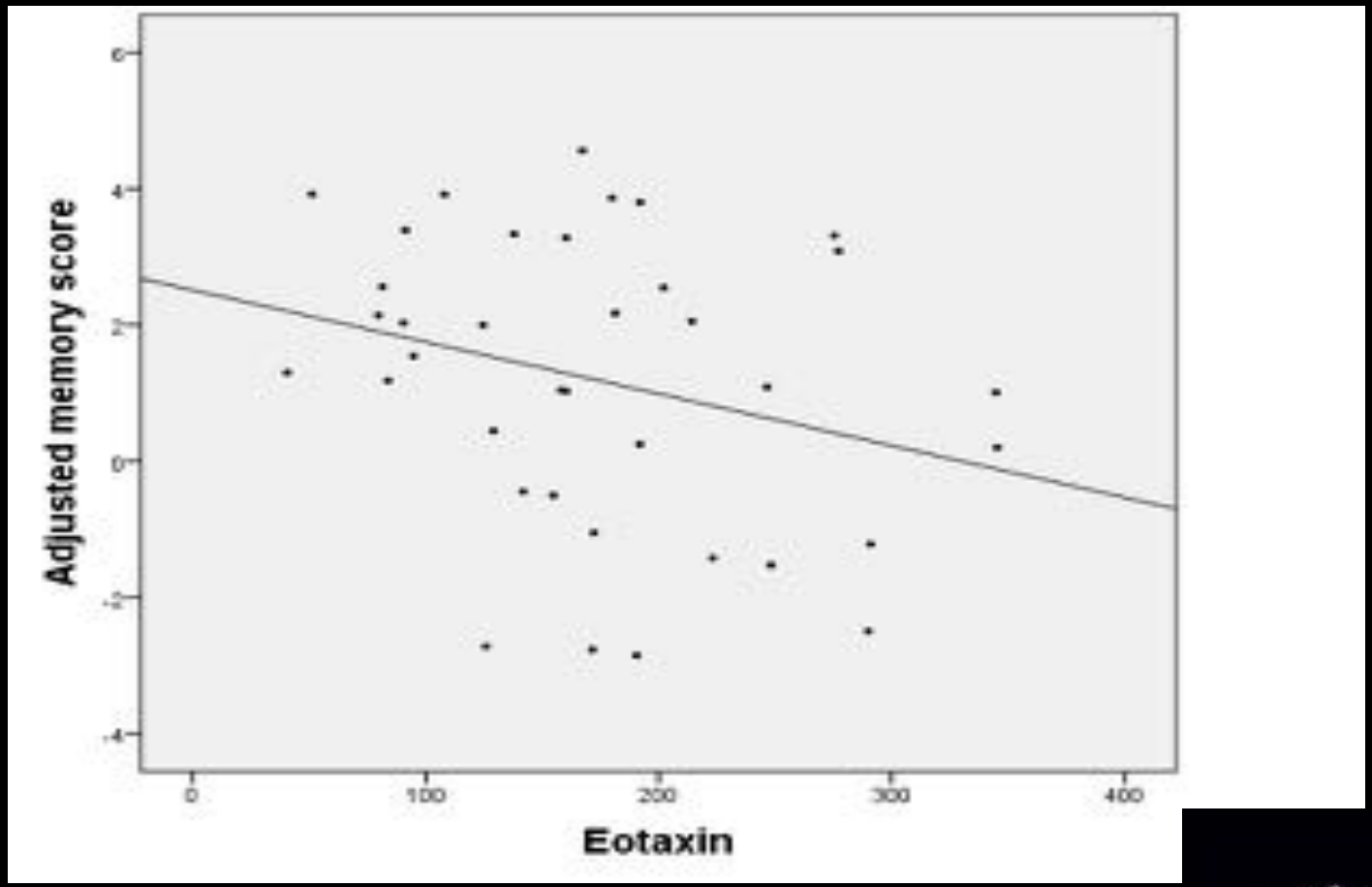


Villeda et al., 2011

Eotaxin in humans

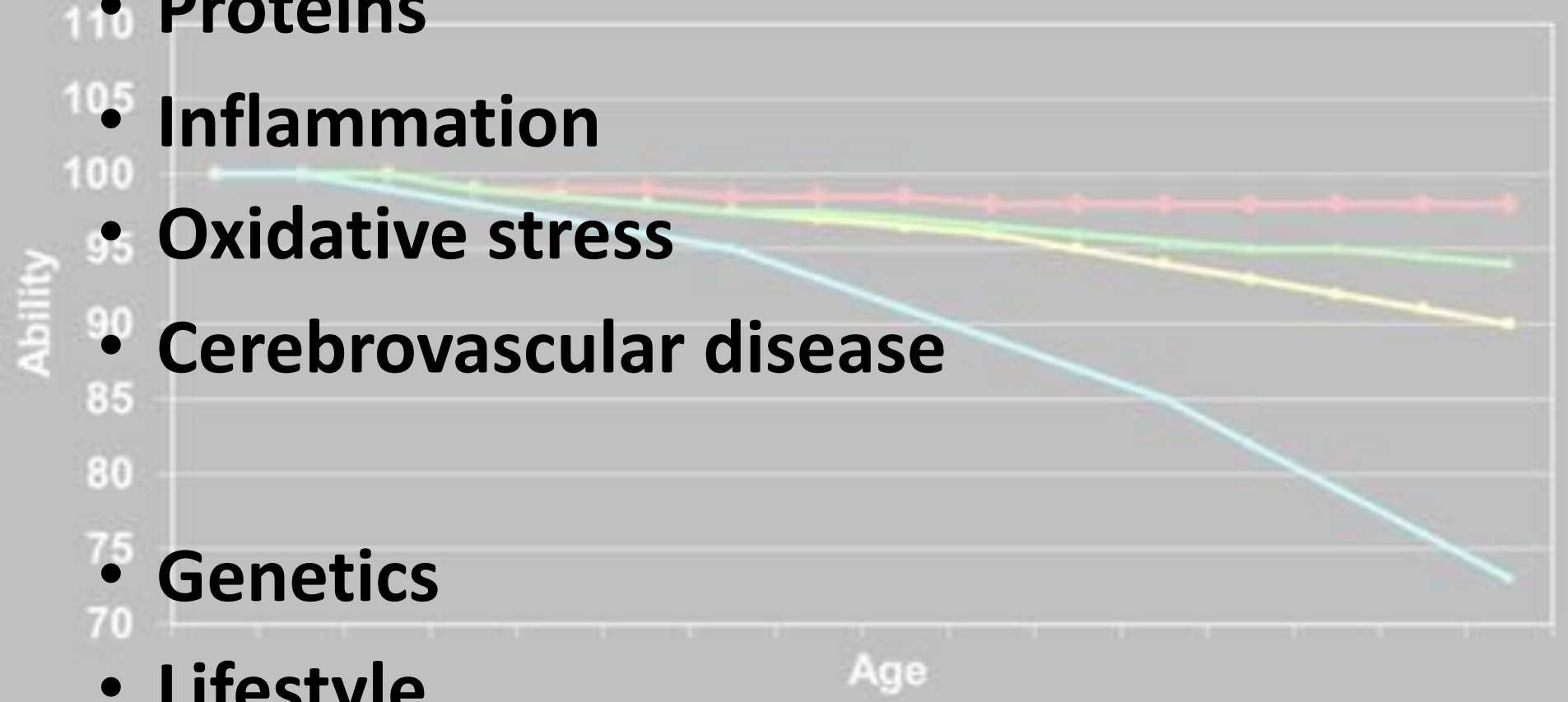


Eotaxin and memory in humans

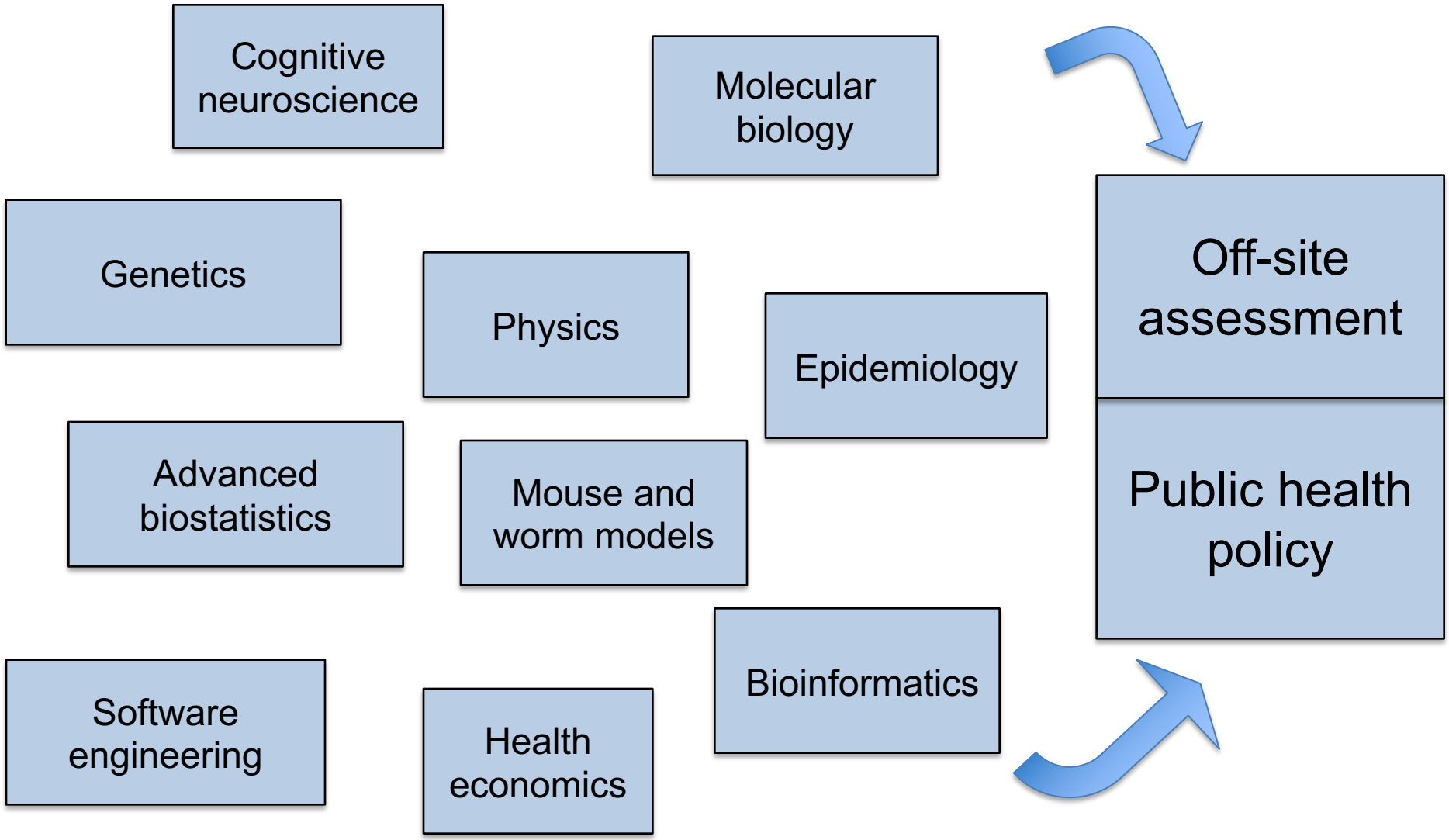


Summary

- Proteins
- Inflammation
- Oxidative stress
- Cerebrovascular disease
- Genetics
- Lifestyle
- Health history



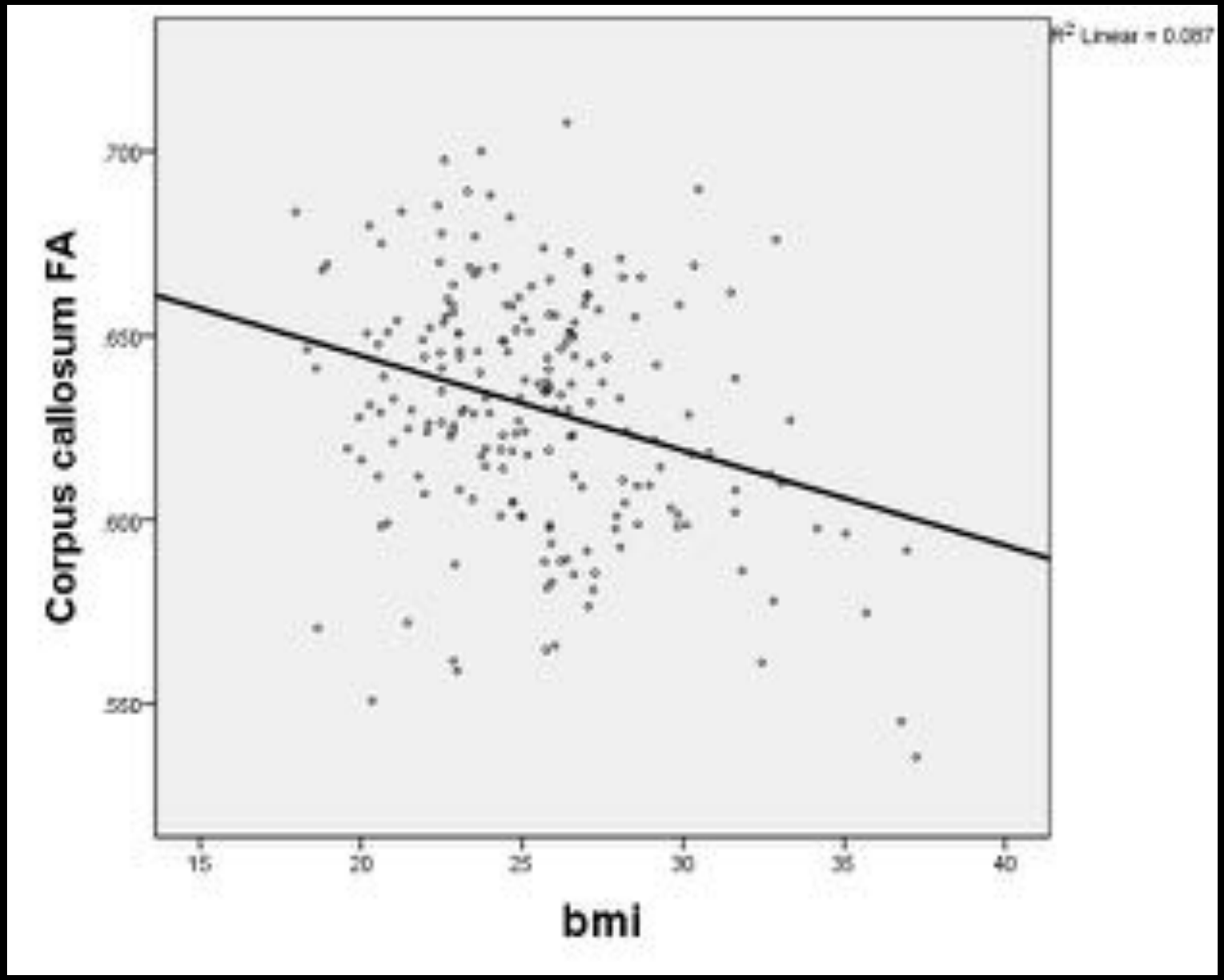
Transdisciplinary convergence



Whitmer & Yaffe

- **36 year follow-up of Kaiser patients who had early measurement of abdominal size and BMI**
  - High BMI (obesity) associated with threefold increase risk of AD and five fold increase in vascular dementia
  - Central obesity (highest quintile) associated with a threefold increase risk of dementia

Body mass and white matter

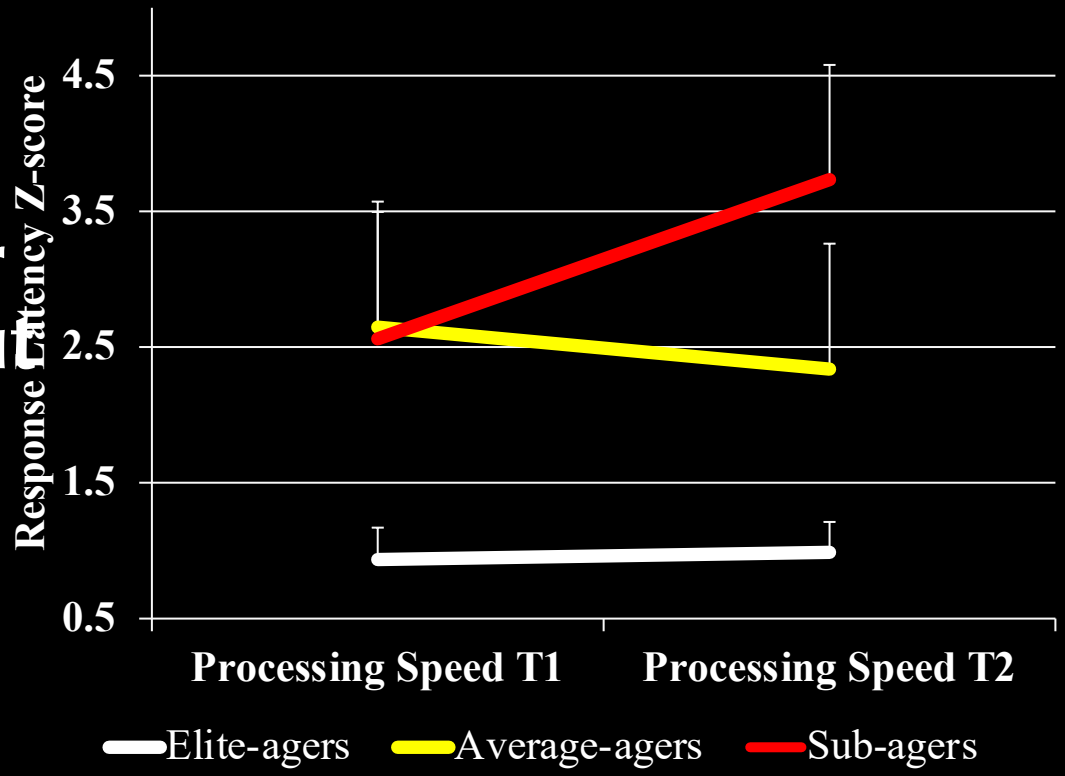


Physical Exercise: Epi studies

- Physical activity, **particularly aerobic activity,** is associated with a significant reduction in risk of dementia.

What can super-agers teach us?

- We can reliably measure declines in processing speed over 2-3 years
- Studying the extremes of this variability can offer valuable clues about mechanisms



Results

- No groups differences were found in BMI, cholesterol, or APOE genotype.

Fractional anisotropy of the corpus callosum

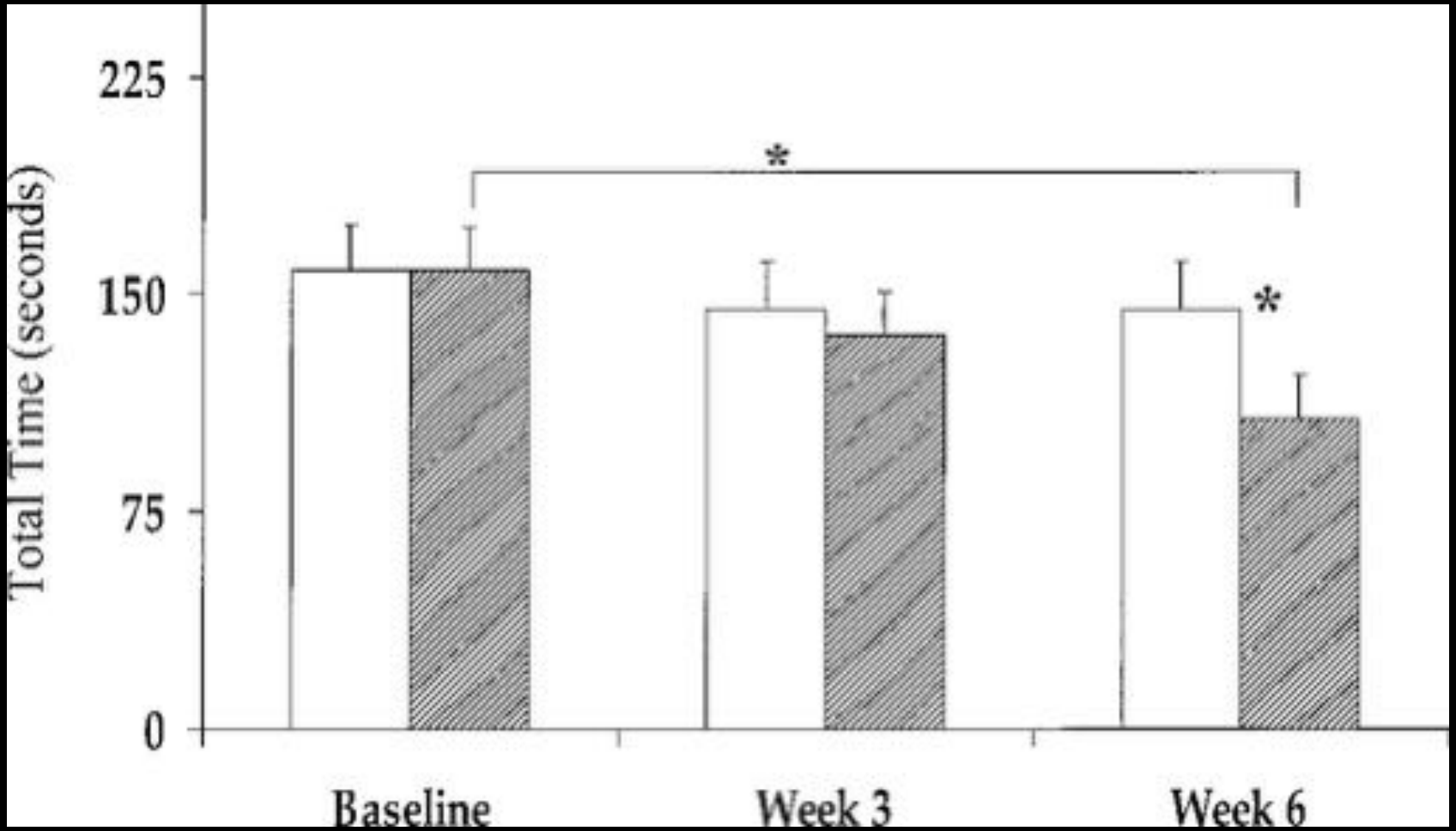
Cardiopulmonary fitness

We can estimate cardiopulmonary fitness using measures of physical activity, BMI, and heart rate

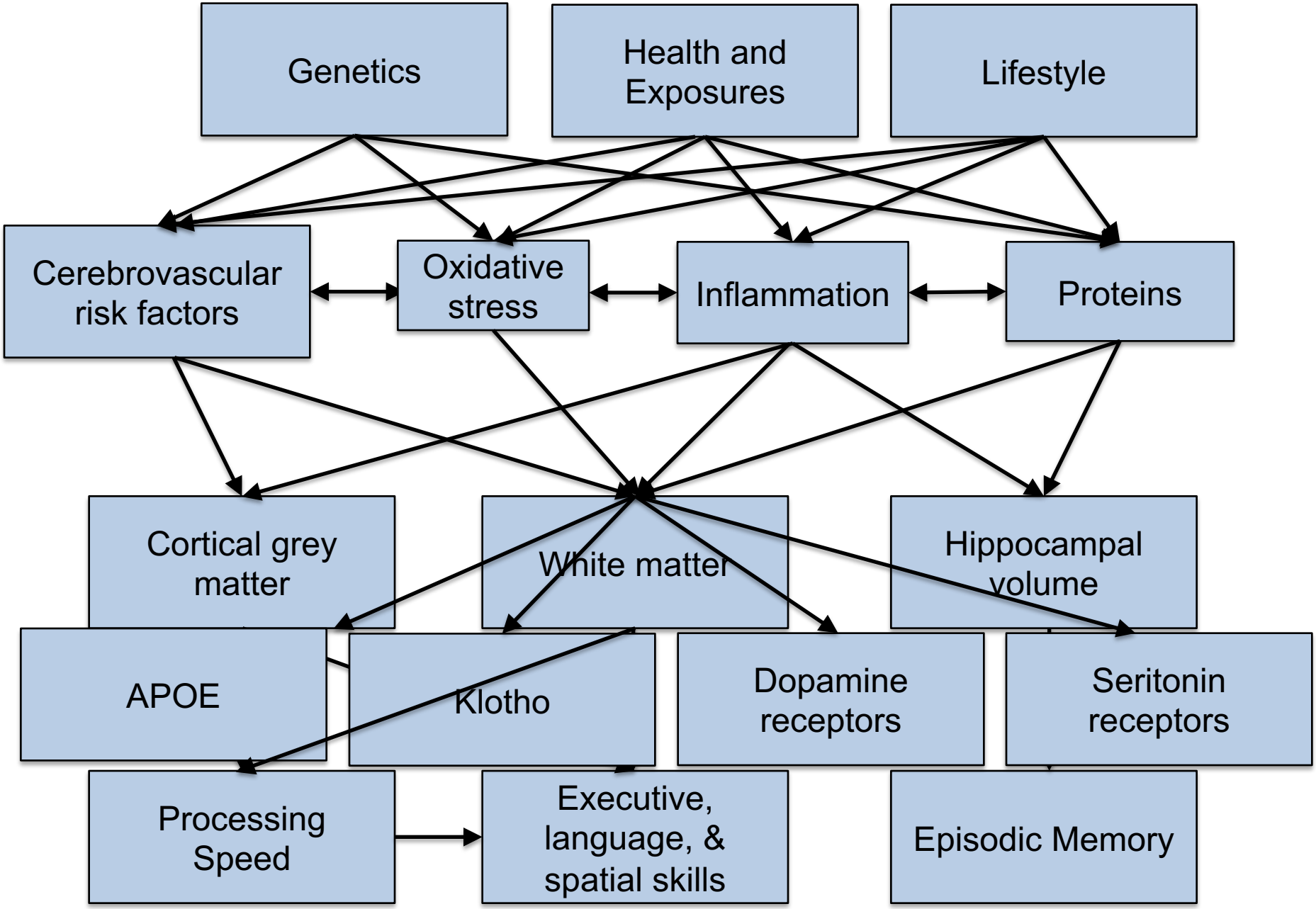
Vision

- Annual wellness visits will include cognitive test results, structural and molecular neuroimaging, proteomics, vascular and other risks, health-related behaviors, and genomic profile.
- This information will identify risks for current and future problems with brain structure or function and lead to targeted, patient-specific interventions.

Block Design in older men treated with testosterone vs placebo



Cherrier et al., 2001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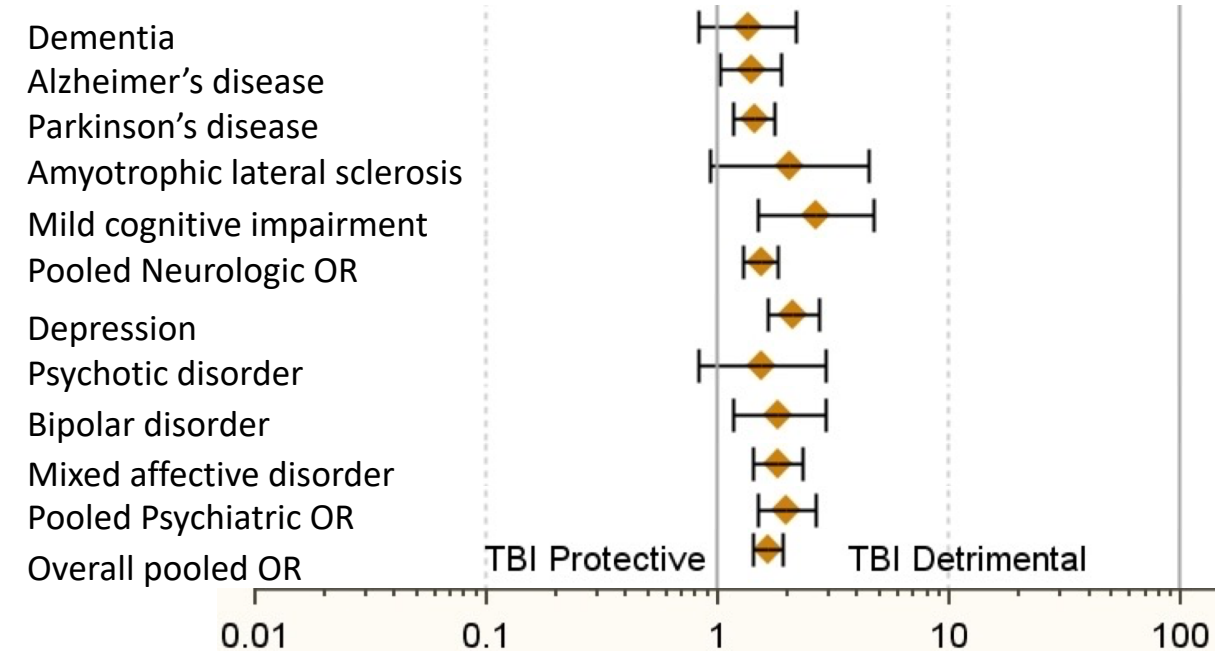
Cortical grey matter
White matter
Hippocampal volume
APOE
Klotho
Dopamine receptors
Seritonin receptors
Processing Speed
Executive, language, & spatial skills
Episodic Memory

Meta-analysis of association between mild TBI and late neurologic/psychiatric diagnoses



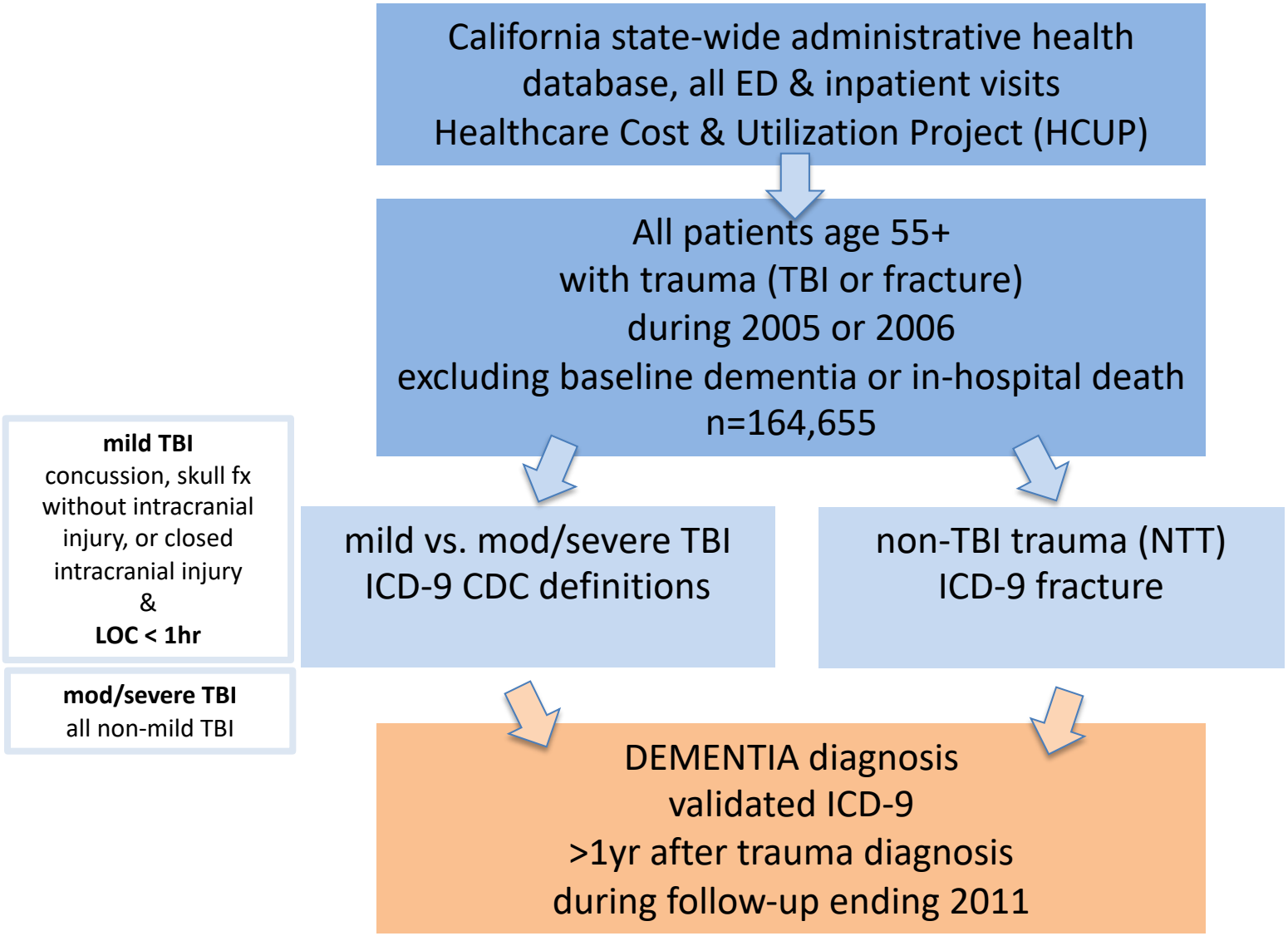
- Meta-analysis positive (1.67) but..
  - low OR, many other factors likely
  - OR for pesticide exposure and PD is 1.94
  - OR for obesity and AD is 1.80

Perry et al, Journal of Neurosurgery (in press)

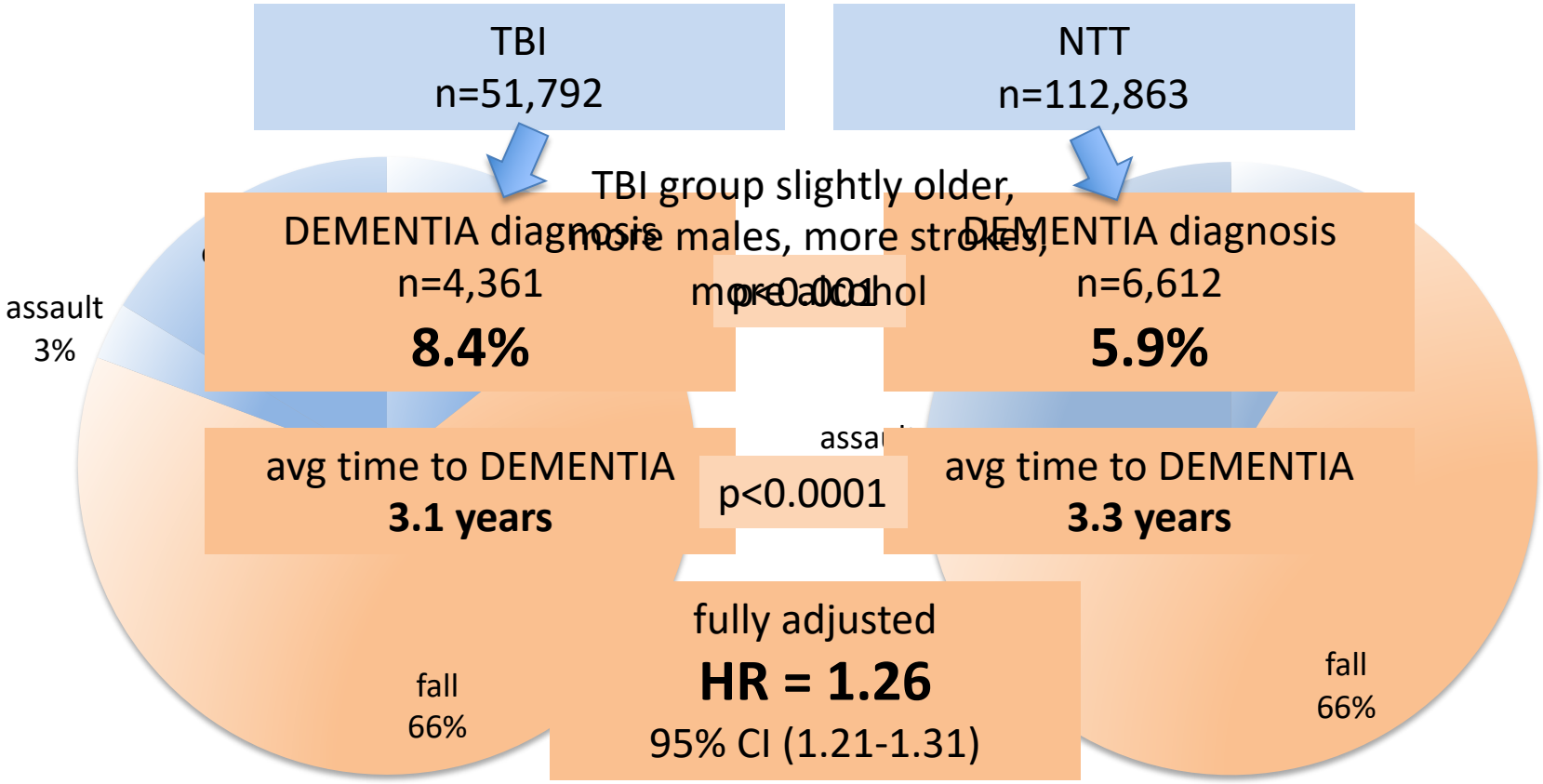
Raquel Gardner

1. Quantify risk of dementia among middle-aged or older adults with recent TBI **compared to those with non-TBI trauma** (fractures)
2. Assess impact of age and TBI severity on risk of dementia

Methods


California state-wide administrative health database, all ED & inpatient visits
Healthcare Cost & Utilization Project (HCUP)
All patients age 55+
with trauma (TBI or fracture)
during 2005 or 2006
excluding baseline dementia or in-hospital death
n=164,655
mild TBI
concussion, skull fx without intracranial injury, or closed intracranial injury
&
LOC < 1hr
mod/severe TBI
all non-mild TBI
mild vs. mod/severe TBI
ICD-9 CDC definitions
non-TBI trauma (NTT)
ICD-9 fracture
DEMENTIA diagnosis
validated ICD-9
>1yr after trauma diagnosis
during follow-up ending 2011

Results



TBI diagnosed at age 55+ is associated with significantly increased risk of dementia over the subsequent 5 - 7 years