CSF biomarkers in aging and the transition to Alzheimer's Disease

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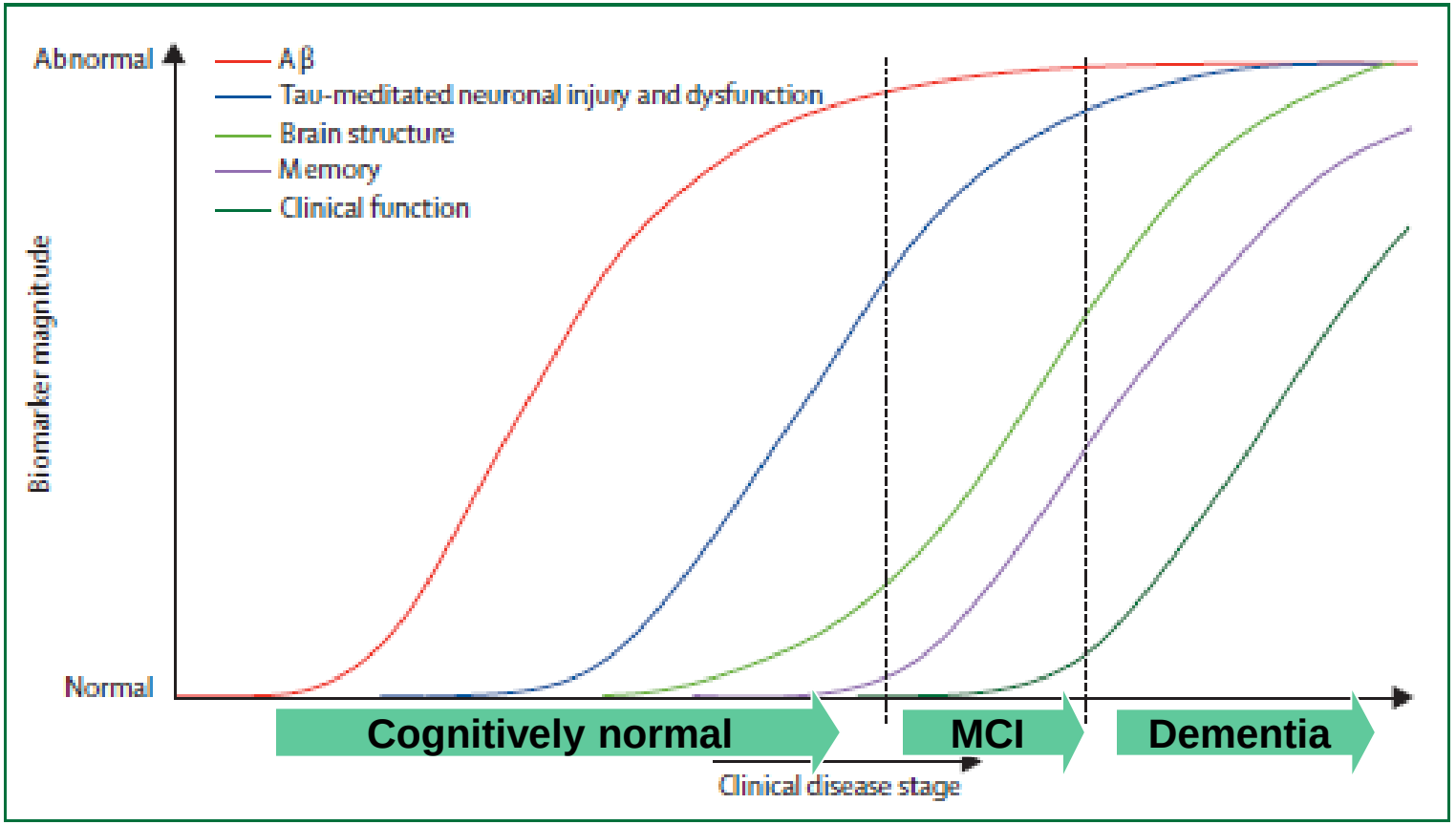
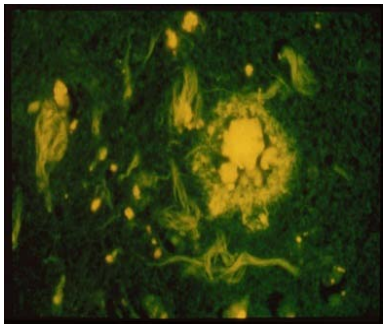
Biomarkers, key AD lesions and symptoms



Jack et al, 2009

Plaques

Tangles



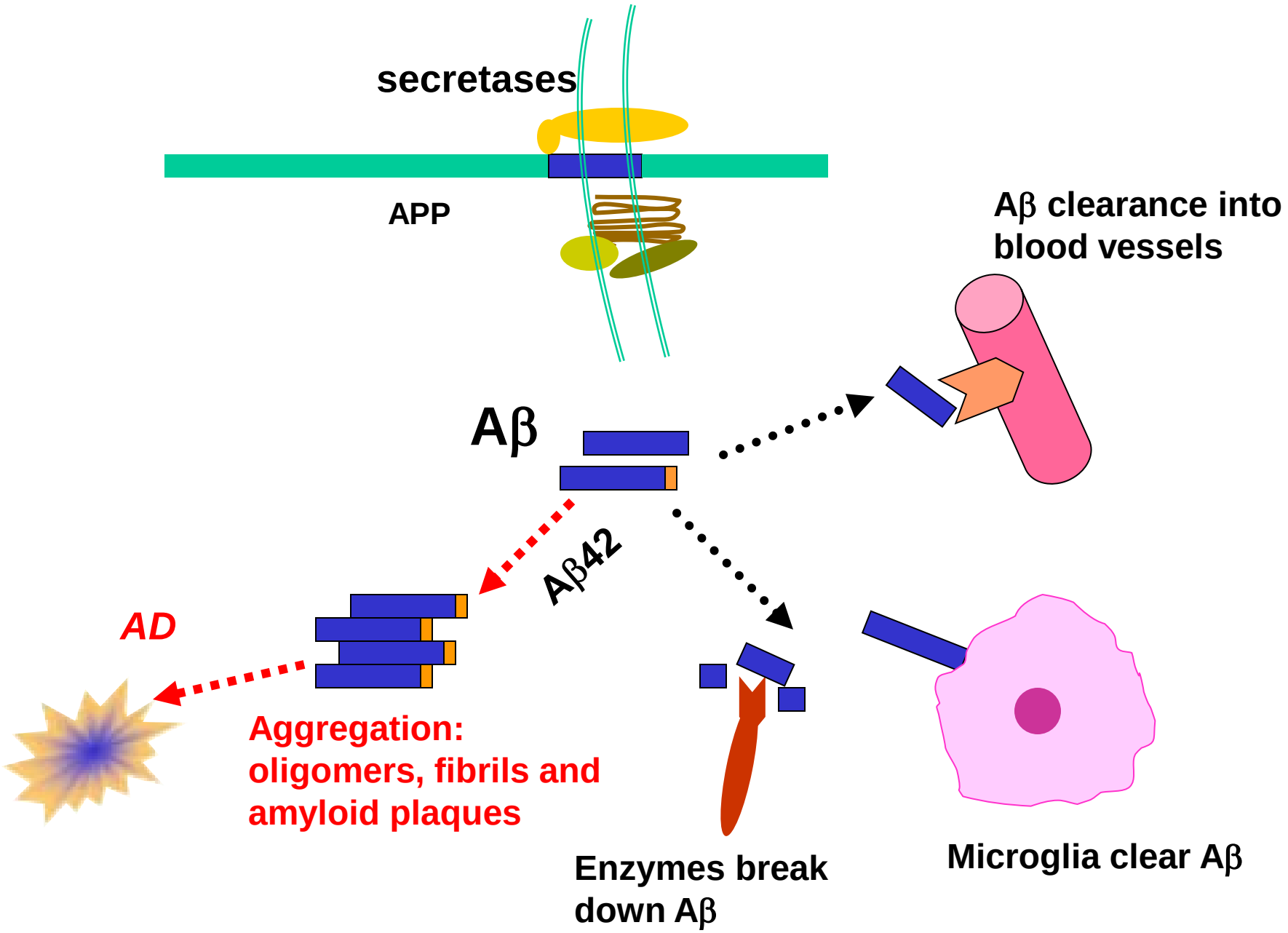
CSF biomarkers and AD

- **Low CSF Aβ42, and high levels of tau and P-tau181** are a core biomarker signature related to AD pathology
- Many studies have defined cutoffs to diagnose AD vs controls, or for differential diagnosis

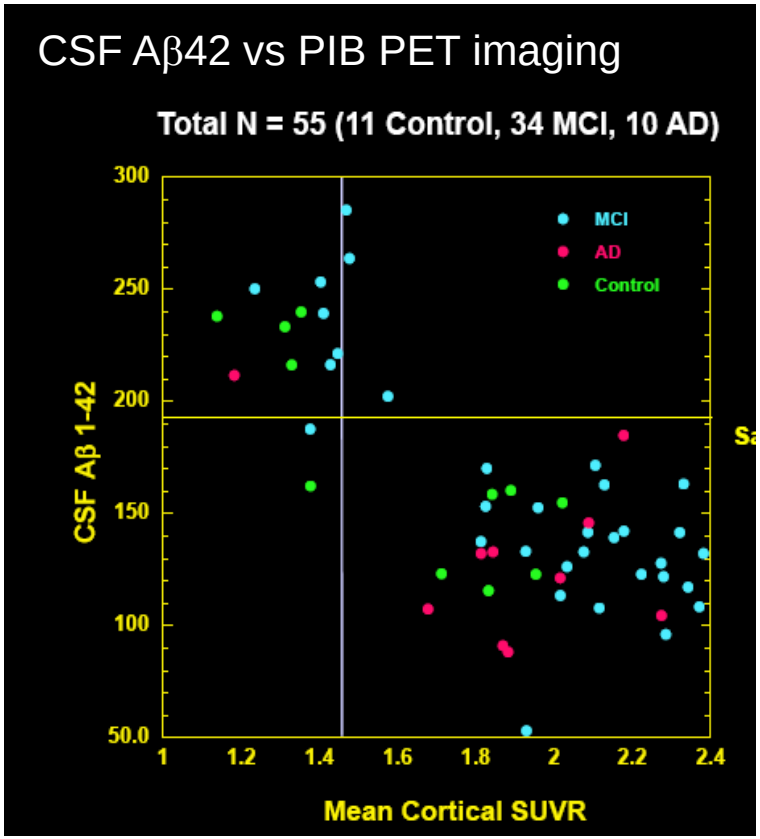
- CSF biomarkers can clarify:
  - timing of the onset of pathology
  - the relationship to brain structural changes and to symptoms
  - pathological mechanisms that may contribute to AD

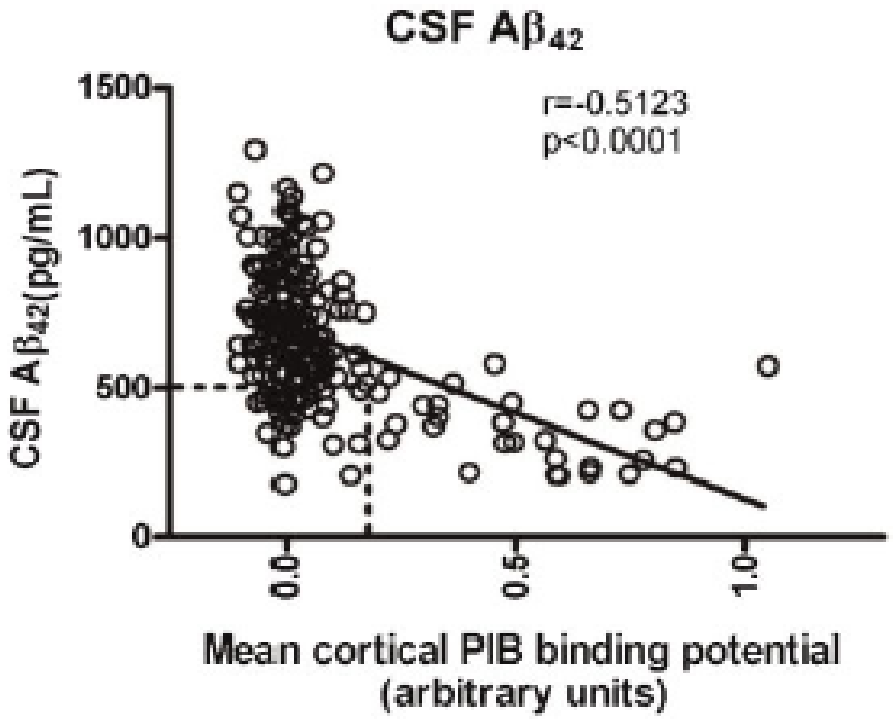
What does the 'concentration' of a biomarker in CSF mean?

- CSF biomarkers turn over, and reflect *recent* brain events
- Markers reach ISF space through
  - secretion e.g. Aβ
  - leakage or damage e.g. tau
- They then undergo clearance:
  - Uptake by cells in the brain
  - Degradation by enzymes
  - Binding to plaques e.g. Aβ42
  - Passage into blood
- Levels of biomarkers in CSF represent an equilibrium between these processes


secretases
APP
Aβ clearance into blood vessels
Aβ
Aβ42
AD
Aggregation: oligomers, fibrils and amyloid plaques
Enzymes break down Aβ
Microglia clear Aβ

Low CSF Aβ42 in AD is related to amyloid deposition





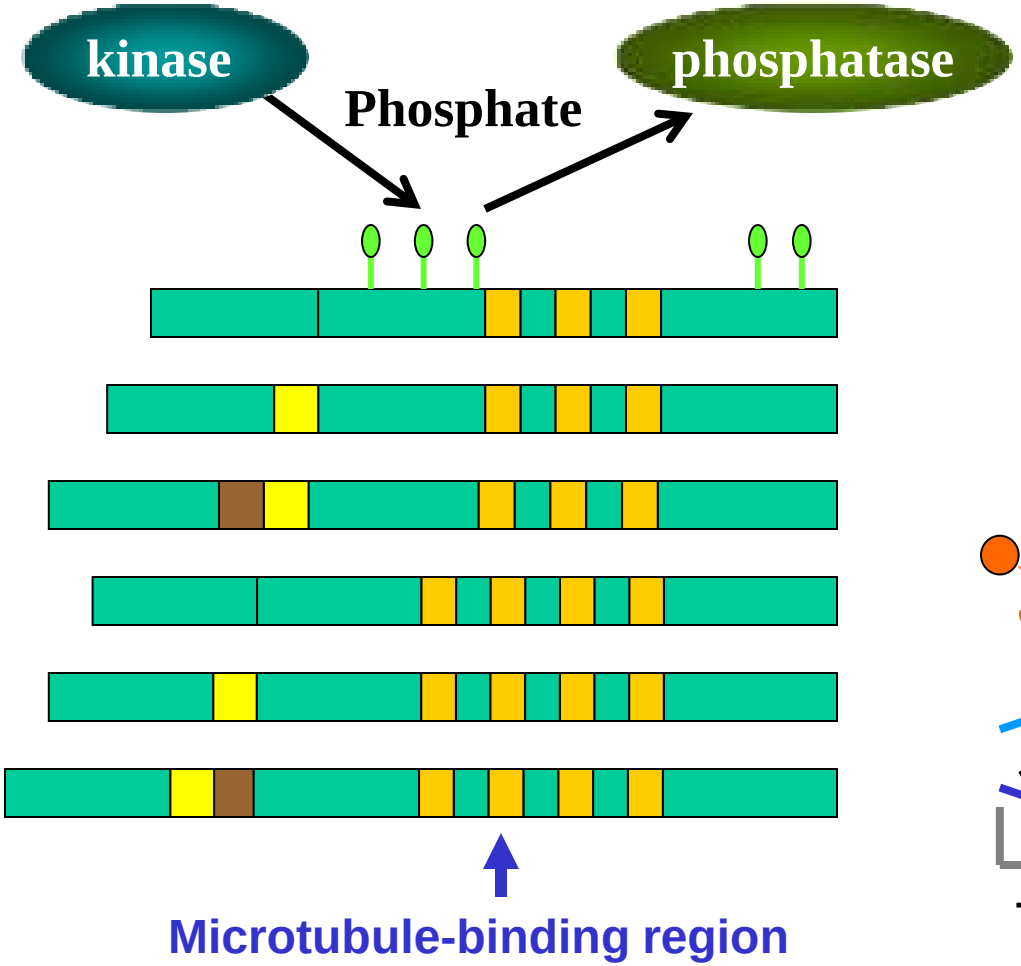
Lower CSF Aβ42 is associated with higher firbillar amyloid amyloid burden (PIB)

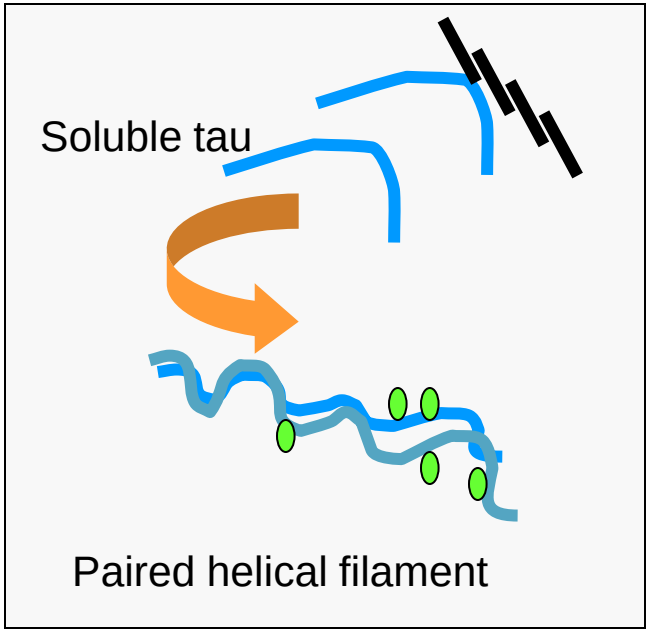
- Fagan et al, 2006; 2008, Rabinovici et al, 2009

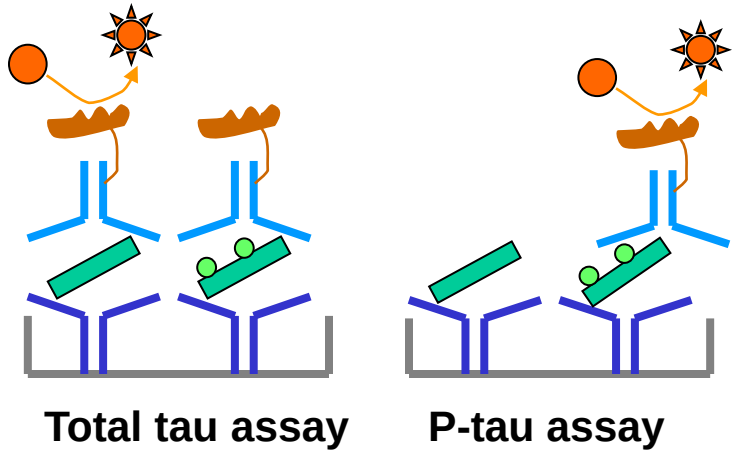
About 14% of normal subjects are PIB neg, but have low CSF Aβ42 ? variability of CSF, *or* pre-fibrillar Aβ e.g. diffuse deposits

- Fagan et al, 2010

Tau and tangles

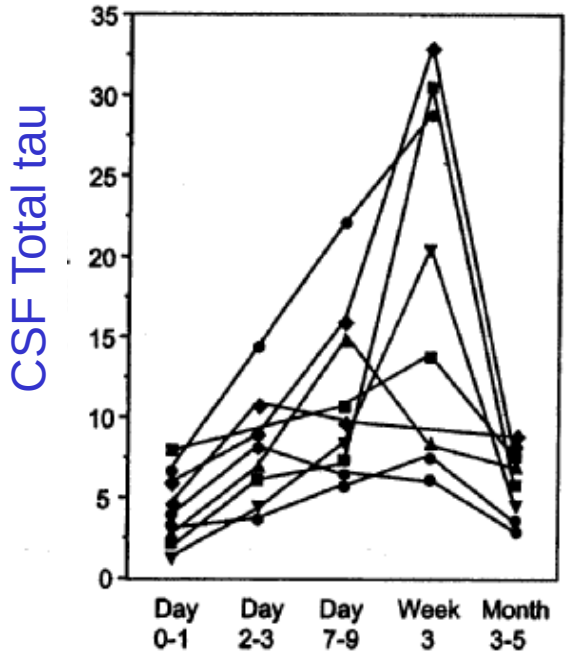


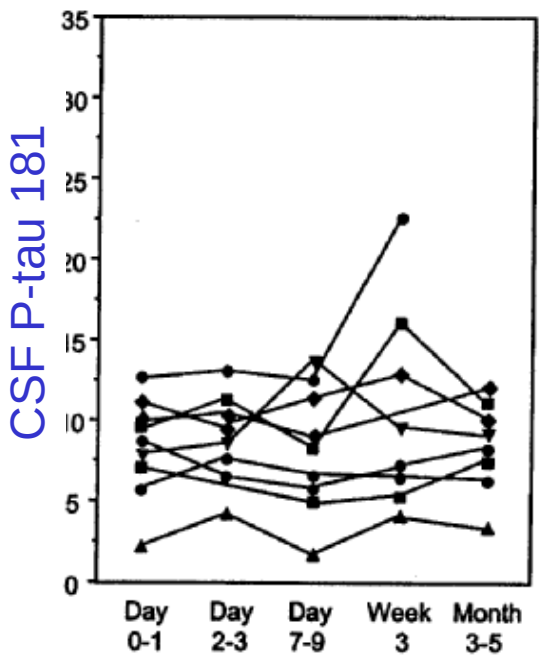




CSF total tau and P-tau

- 2-3 fold ↑ in AD vs controls; sensitivity 75-85%
- Levels not related to APO-E genotype or dementia severity
- Remains stably ↑ in AD
- Acute damage e.g. stroke, or neuronal death e.g. CJD, leads to marked ↑ total tau, not P-tau





CSF Tau increases after stroke, P-tau181 does not

Hesse, 2001

A CSF study across the adult lifespan

- Funded as NACC Collaborative project: UCSD,
  J, U Penn

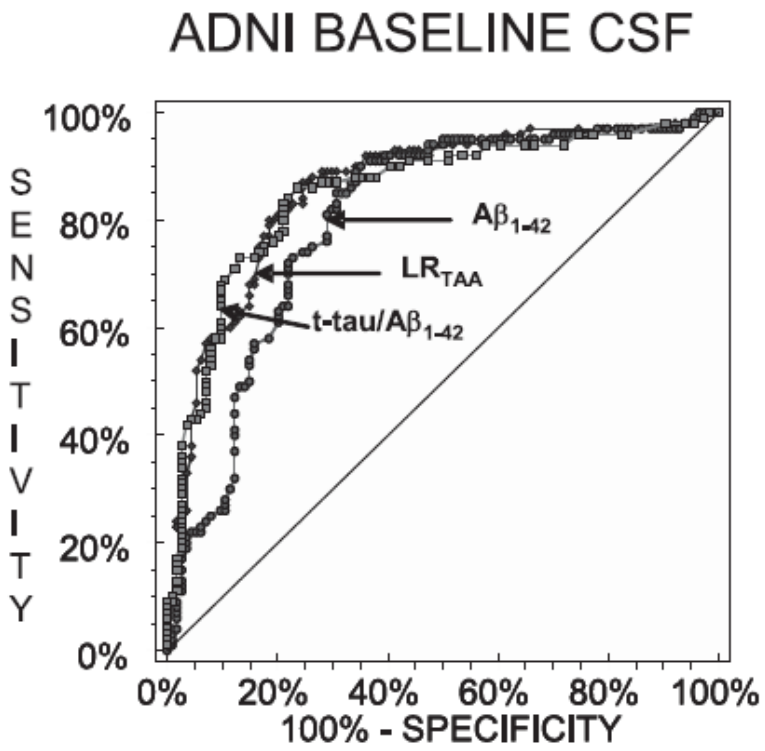
  fill age strata
  MMSE > 27/30, normal on NYU

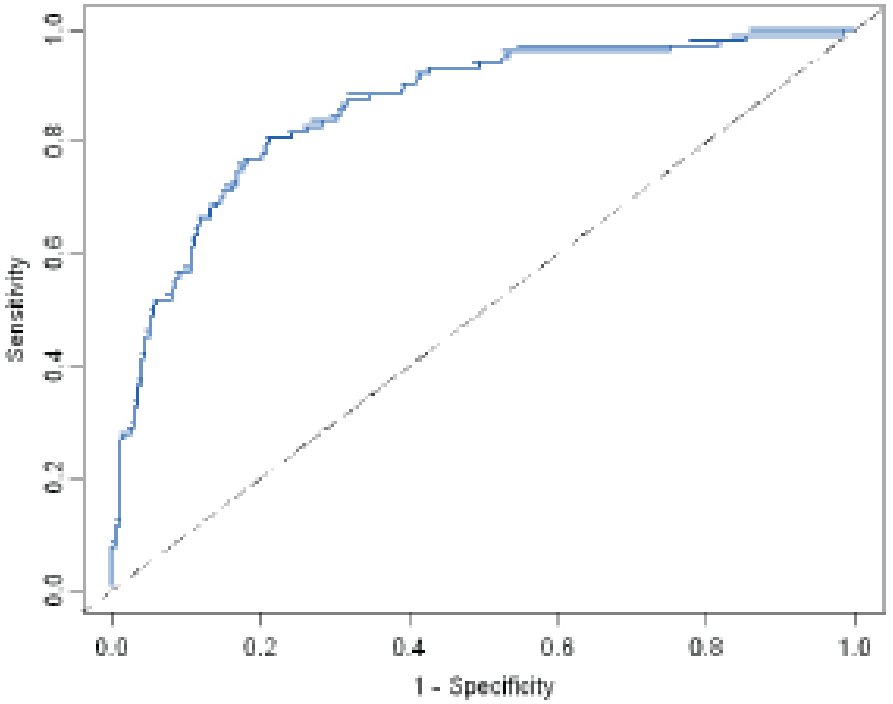
  ammatory illnesses
  ecting CNS
  ness, major organ failure,
  ucose and platelet count

Demographics and biomarker levels

	Controls < 60	**Controls, ≥ 60**	**AD**
Number	155	145	104
Age	41 ± 3.0	72 ± 7.2	72 ± 9.2
Sex (% F)	54	54	46
Education	16 ± 2.7	16 ± 2.7	16 ± 3.2
APO-E e4+ (%)	38	28	69
Body Mass Index	24 ± 3.2	26 ± 3.4	26 ± 3.3
CSF Aβ42	274 ± 41	236 ± 67	157 ± 54
CSF Tau	54 ± 14	71 ± 24	105 ± 37
CSF P-tau181	26 ± 8	33 ± 14	51 ± 18

Comparisons between **AD** and controls





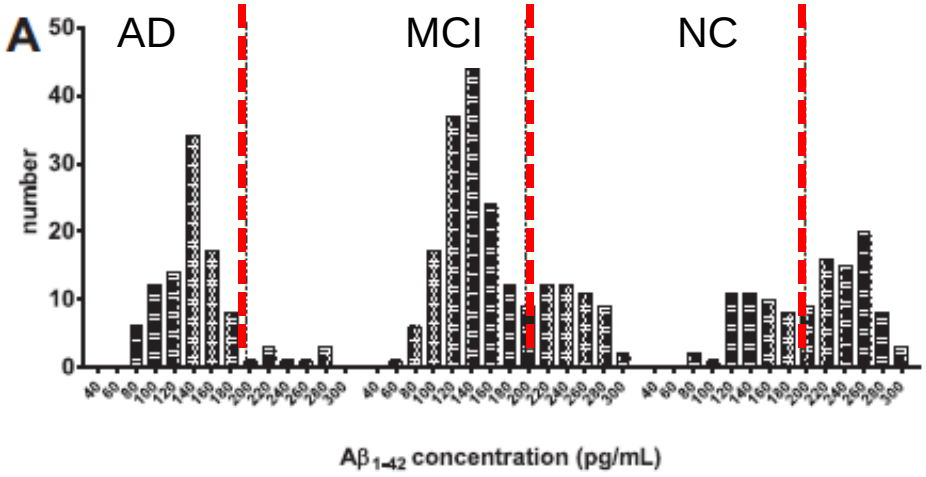
Tau / Aβ42: AUC = 0.90,
sens = 87%, spec 85 %

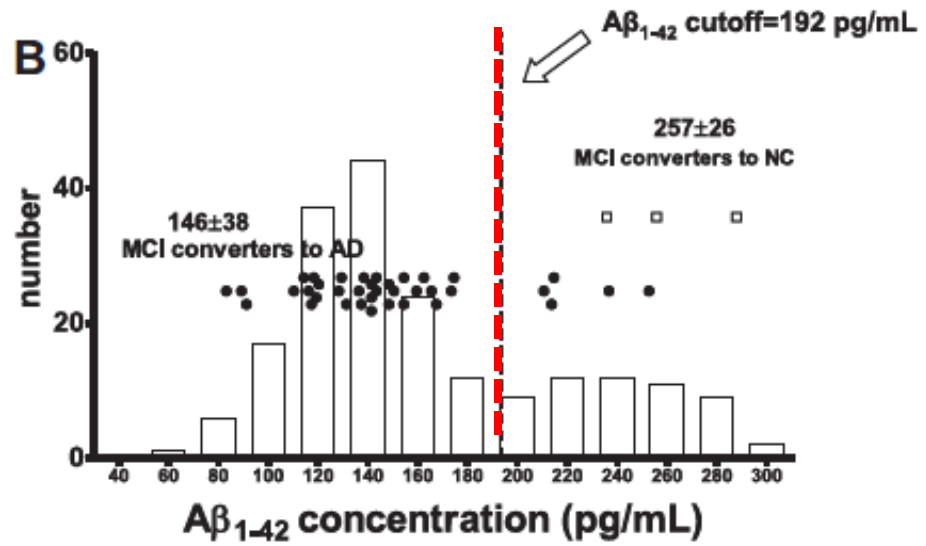
Shaw et al, 2009

Tau / Aβ42: AUC = 0.84,
Sens = 86%, spec 75 %

Galasko et al, ICAD 2008

MCI, CSF biomarkers and the Alzheimer's Disease Neuroimaging initiative (ADNI)



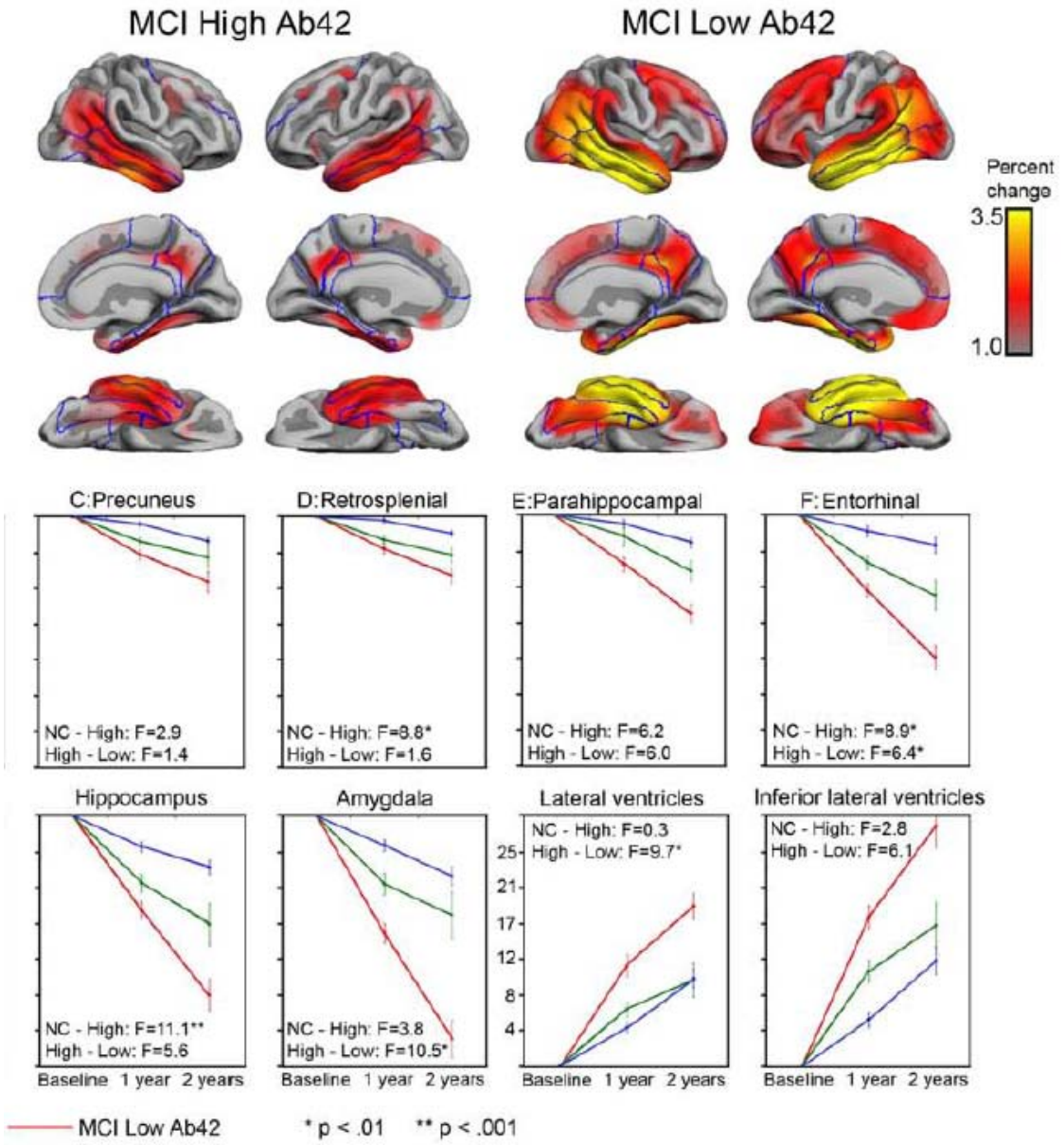


Cutoffs for Aβ42, tau and P-tau181 came from a cohort of autopsy-proven AD and elderly controls.

CSF Aβ42 and tau/ Aβ42 predicted which MCI subjects progressed to AD in 12 months.

Shaw et al, 2009

CSF biomarkers and structural MRI in MCI



ADNI MCI subjects with an AD CSF profile showed greater atrophy at baseline and on follow-up

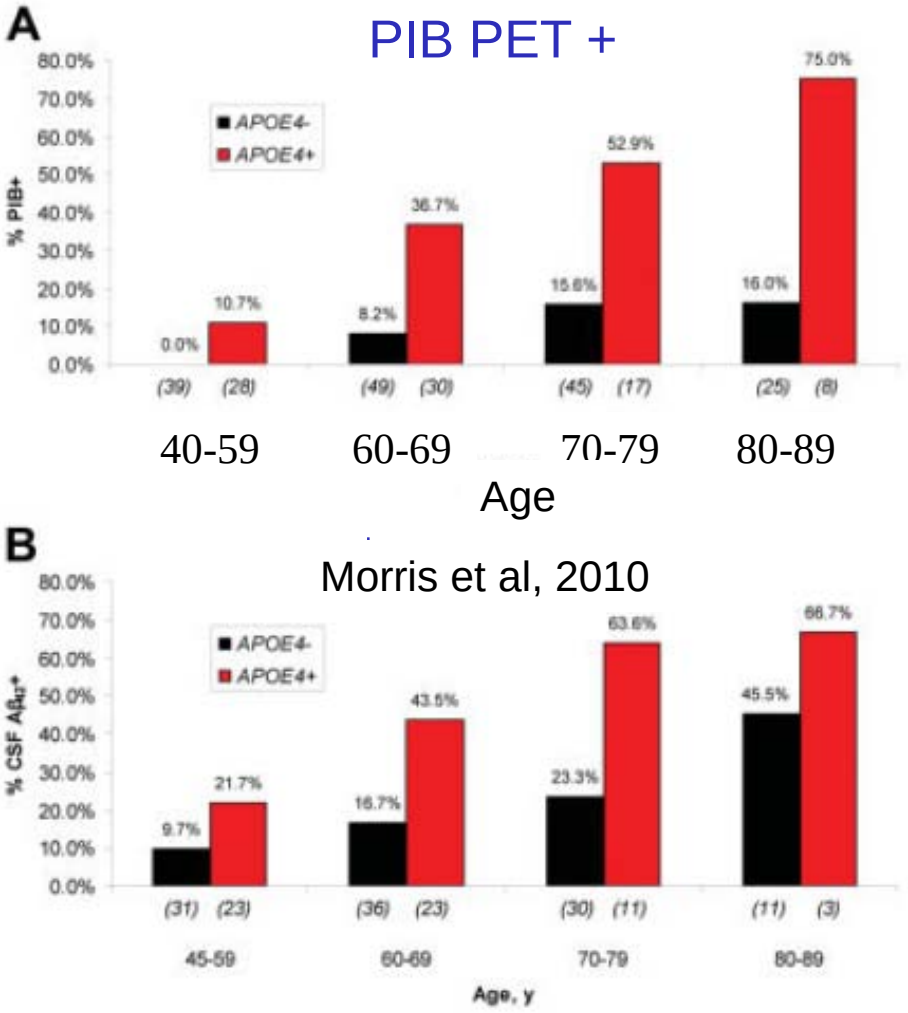
Fjell et al, 2010

Detecting an AD signature in **normals**

- Amyloid pathology is a likely initiating event in AD
- Deposition is followed by a long preclinical buildup of structural changes before symptoms emerge
- A *signature* of pathology in cognitively normal subjects should meet the following predictions:
  - Resembles the signature in AD-dementia
  - Increased frequency with age
  - Increased in genetically predisposed subjects
  - Predicts cognitive decline and progression to MCI and AD

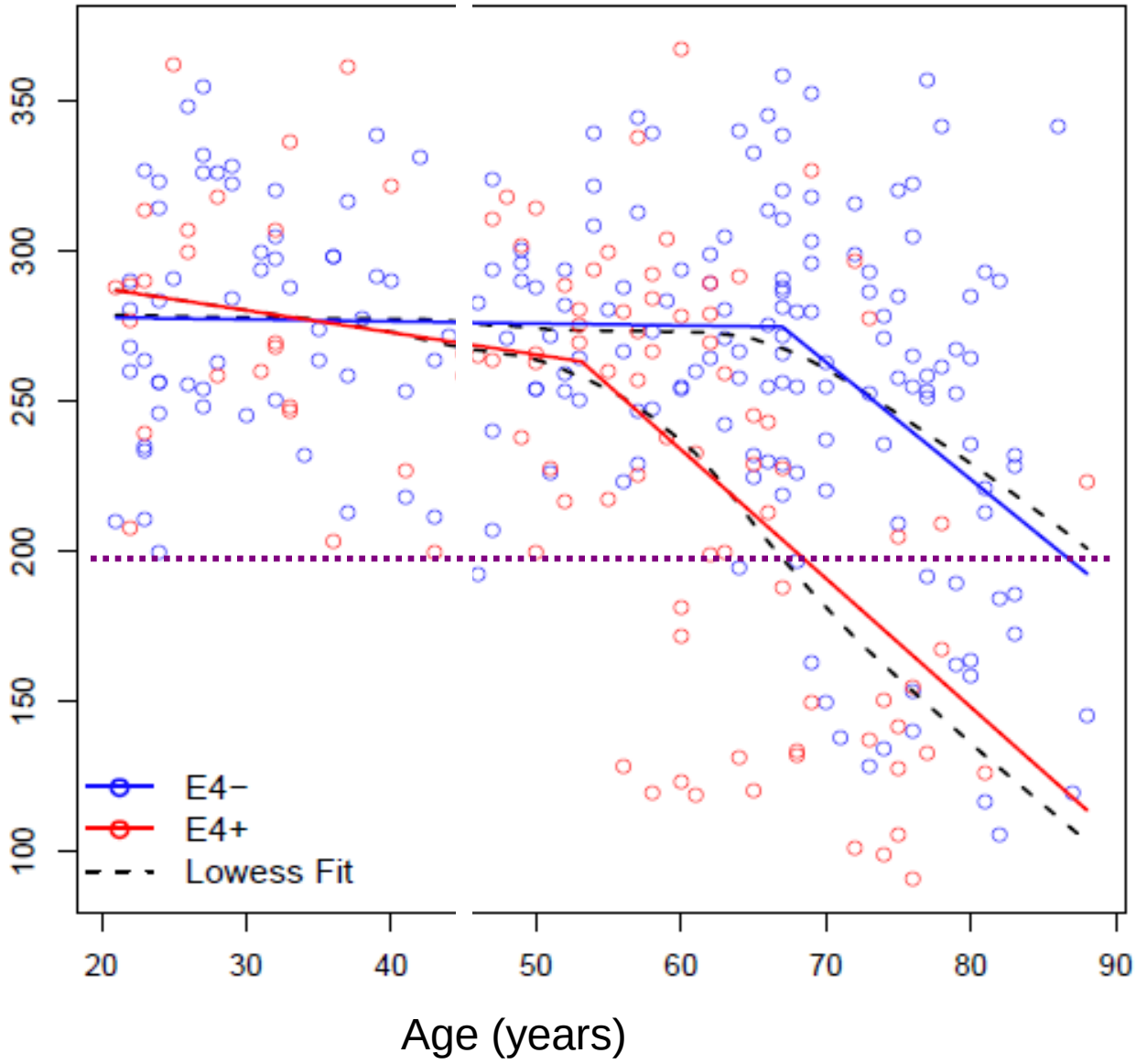
Age, APO-E e4 and amyloid biomarkers

	Age of normal subjects	% with AD CSF
ADNI	76 ± 5	31 - 38
DESCRIPA normal	67 ± 6	31
complaints	66 ± 8	52
Galasko et al	67 ± 10	25

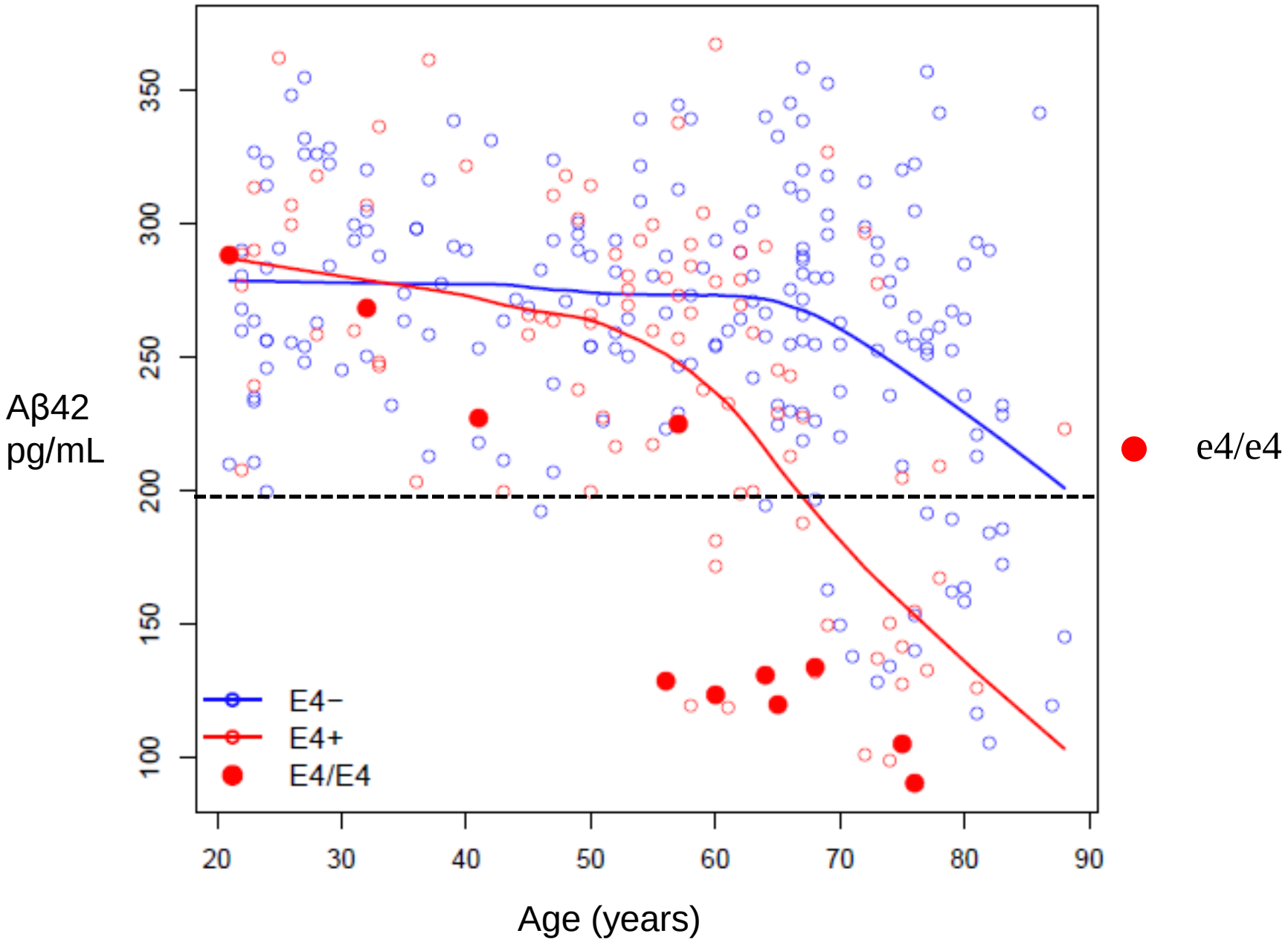


CSF Aβ42 in controls vs age and APO-E e4

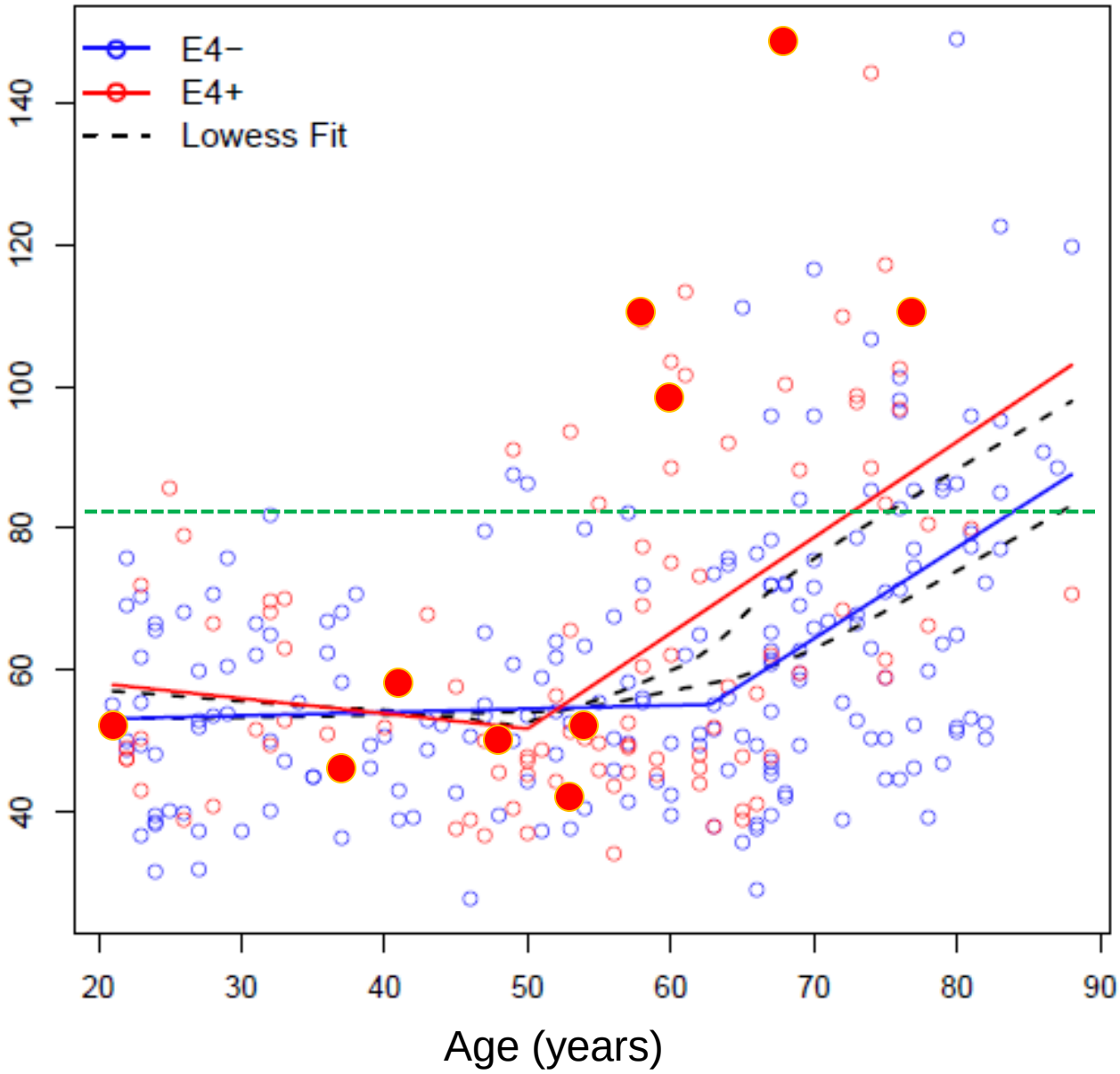
Aβ42
pg/mL



Mean – 2SD,
young NC


Aβ42
pg/mL
350
300
250
200
150
100
20
30
40
50
60
70
80
90
Age (years)
E4−
E4+
E4/E4
e4/e4

CSF T-tau in controls vs age and APO-E e4



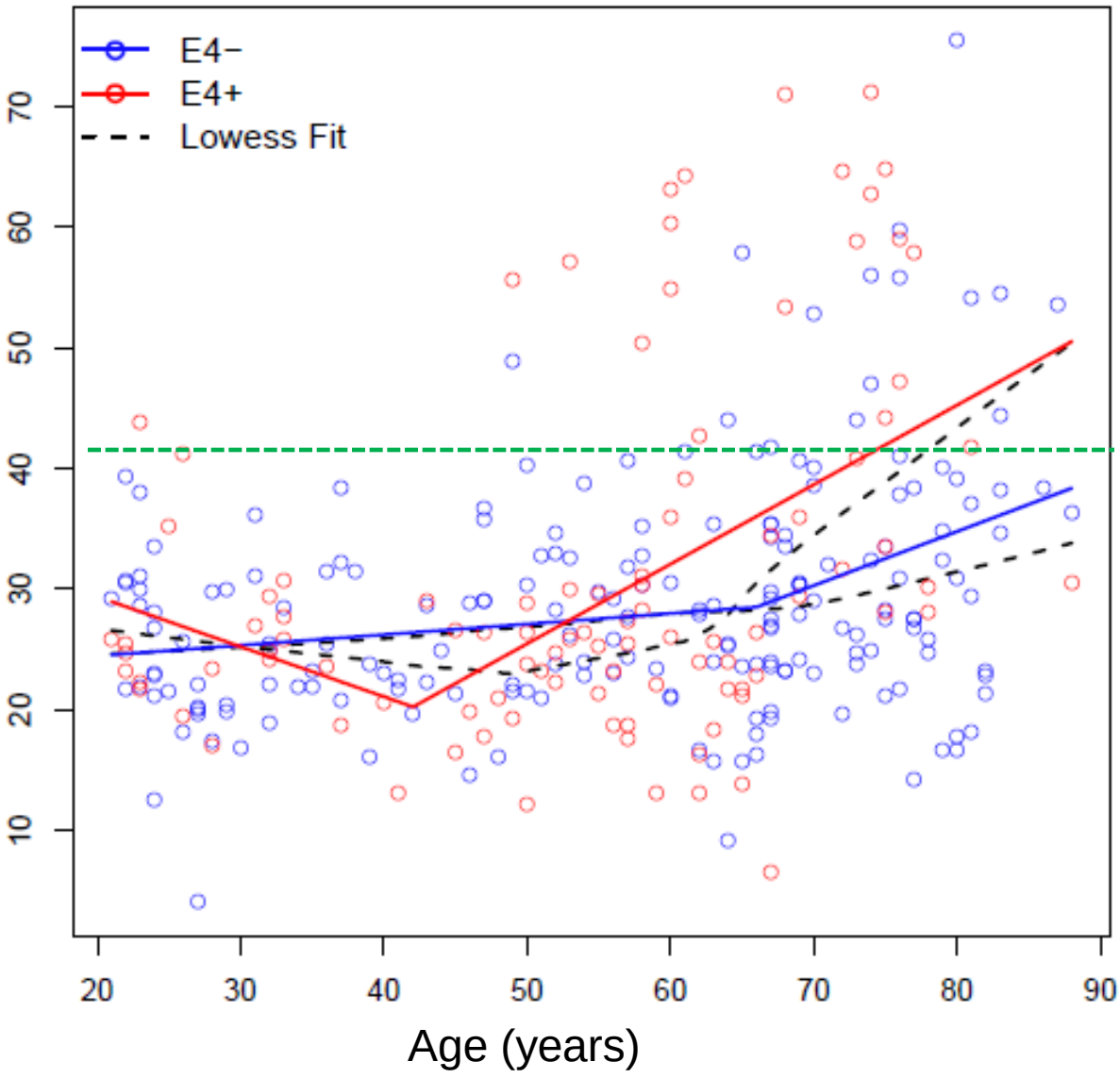
T-tau
pg/mL

e4/e4

Mean ± 2SD,
young NC

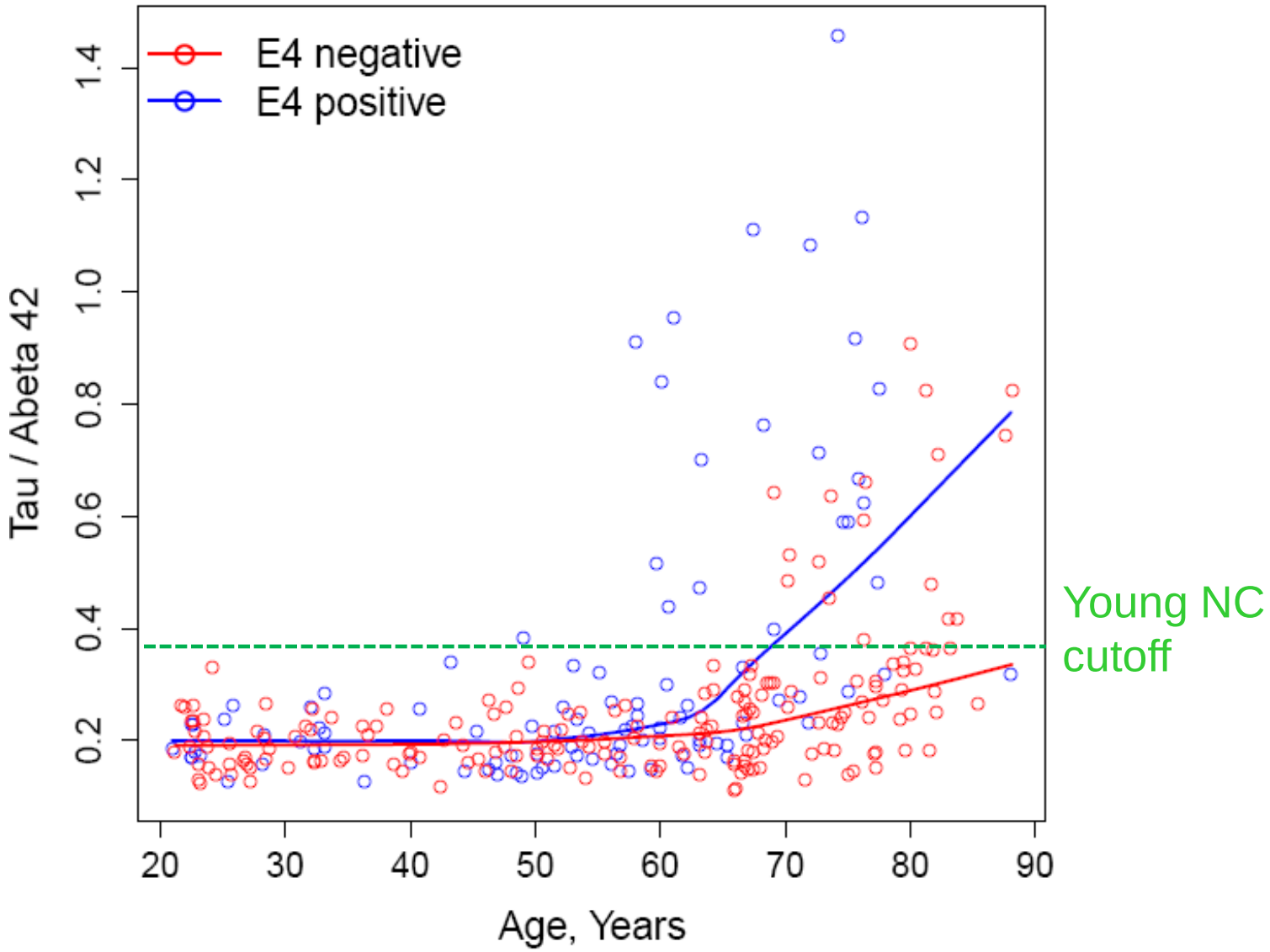
CSF P-tau181 in controls vs age and APO-E e4

P-tau181
pg/mL

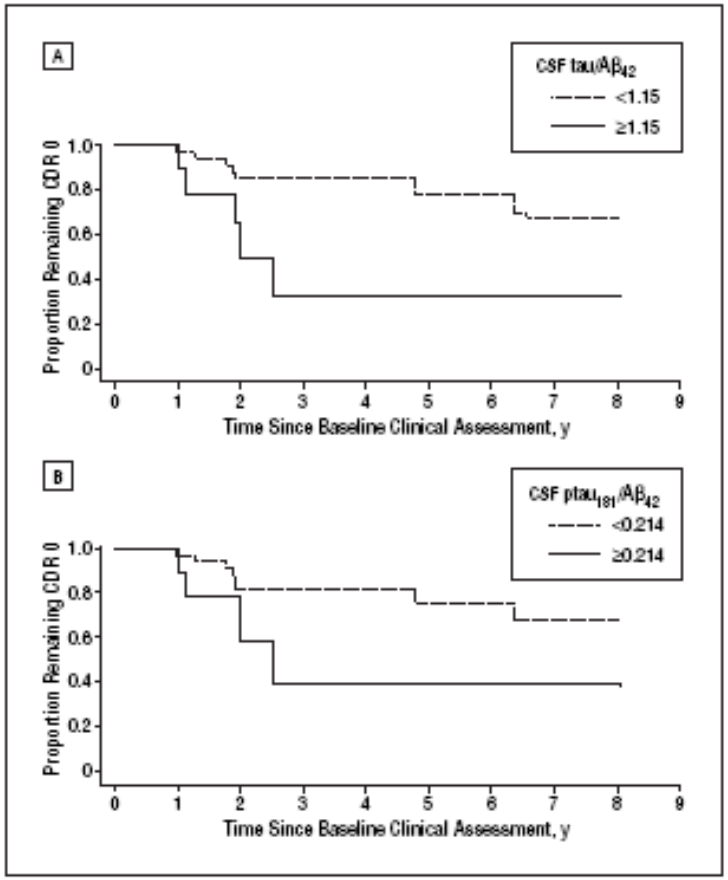


Mean ± 2SD,
young NC

Tau / Aβ42 in controls vs age and APO-E e4



Do CSF biomarkers predict decline in normals?

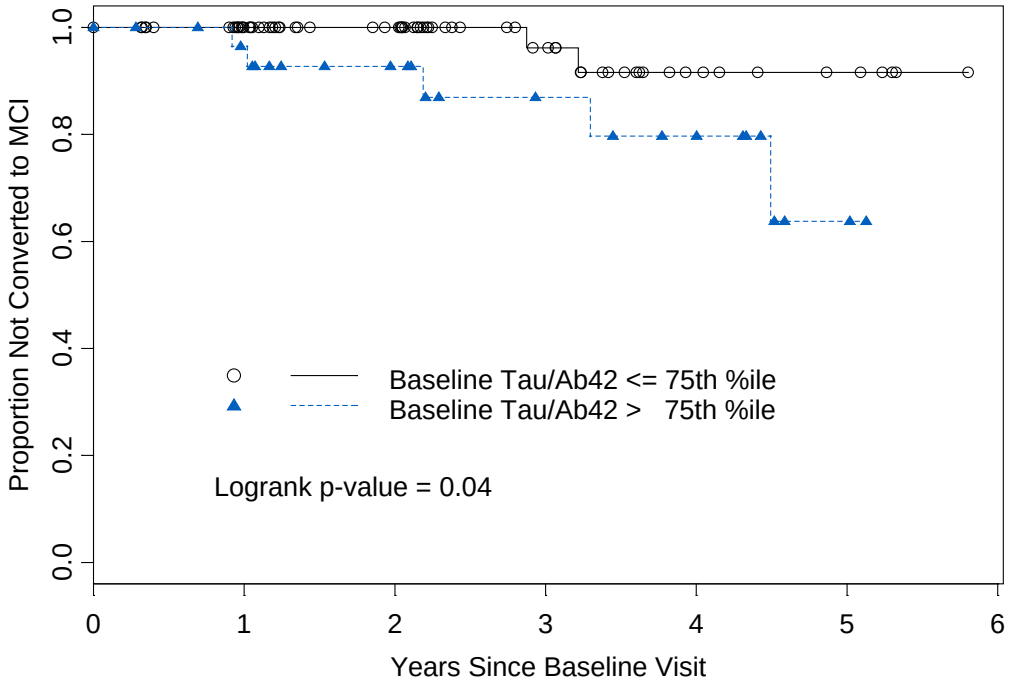


61 subjects, initially CDR 0, mean age 75

HR for progression = 2.4 for tau/Aβ42 and 1.8 for Ptau181/Aβ42

Fagan et al, 2007

Progression to MCI or AD in controls



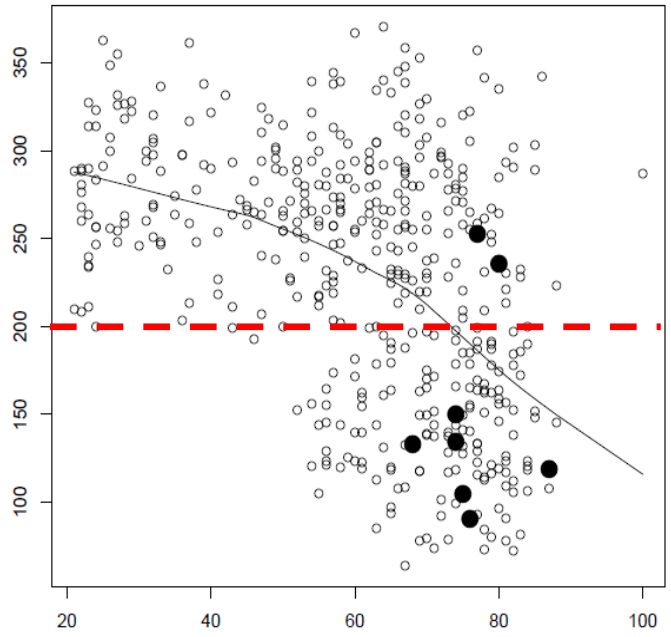
109 controls, mean age 70

HR for progression = 1.6 for tau/Aβ42

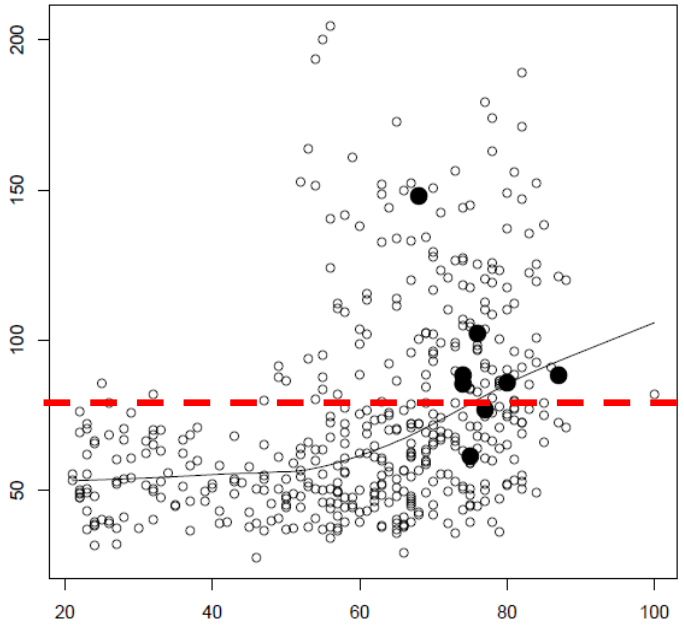
Galasko et al, unpublished

CSF biomarkers in control subjects who progressed

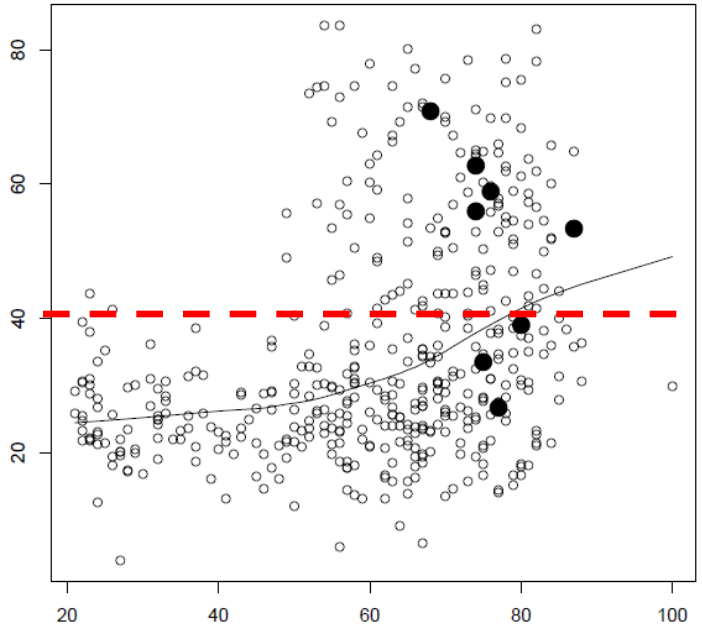
Aβ42



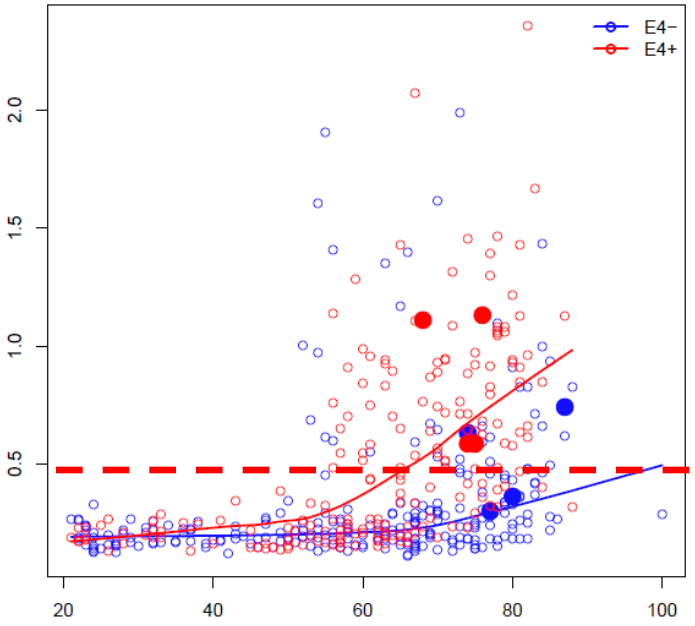
PTau181



Tau



Tau/
Aβ42



Proteomic adventures 2D-DIGE

Craig-Shapiro et al

CSF discovery samples:
AD NC

↓

Immunodeplete 6 highly abundant proteins

↓

Differential dye labels for:
AD **NC** **Pool**
Cy5 **Cy3** **Cy2**

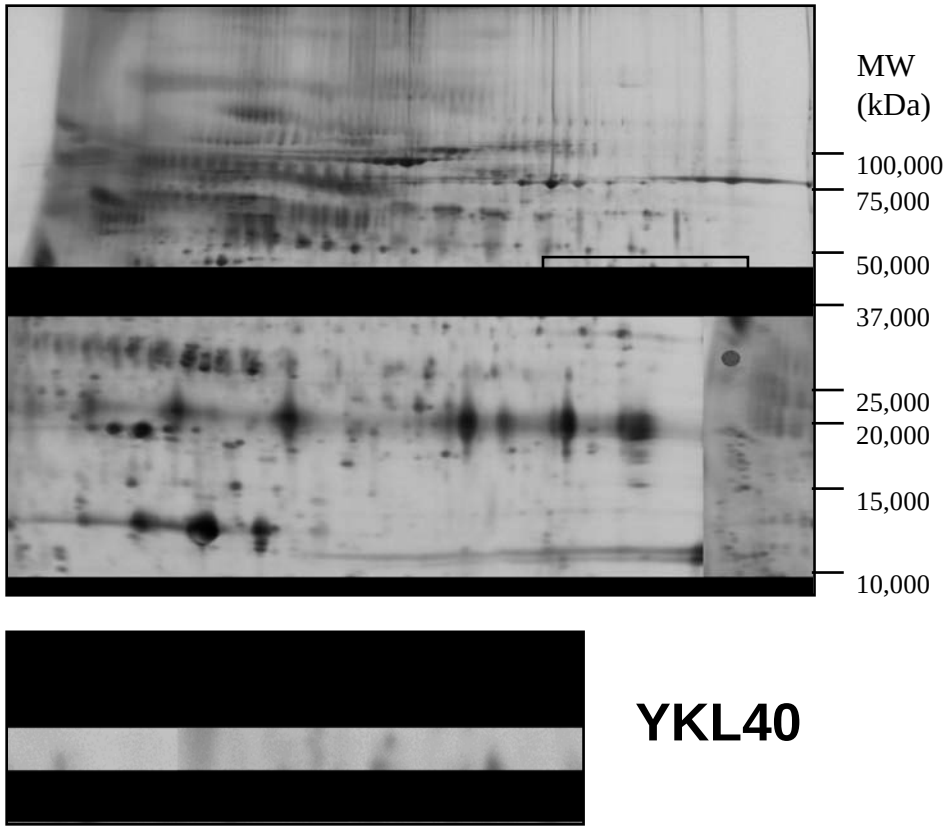
↓

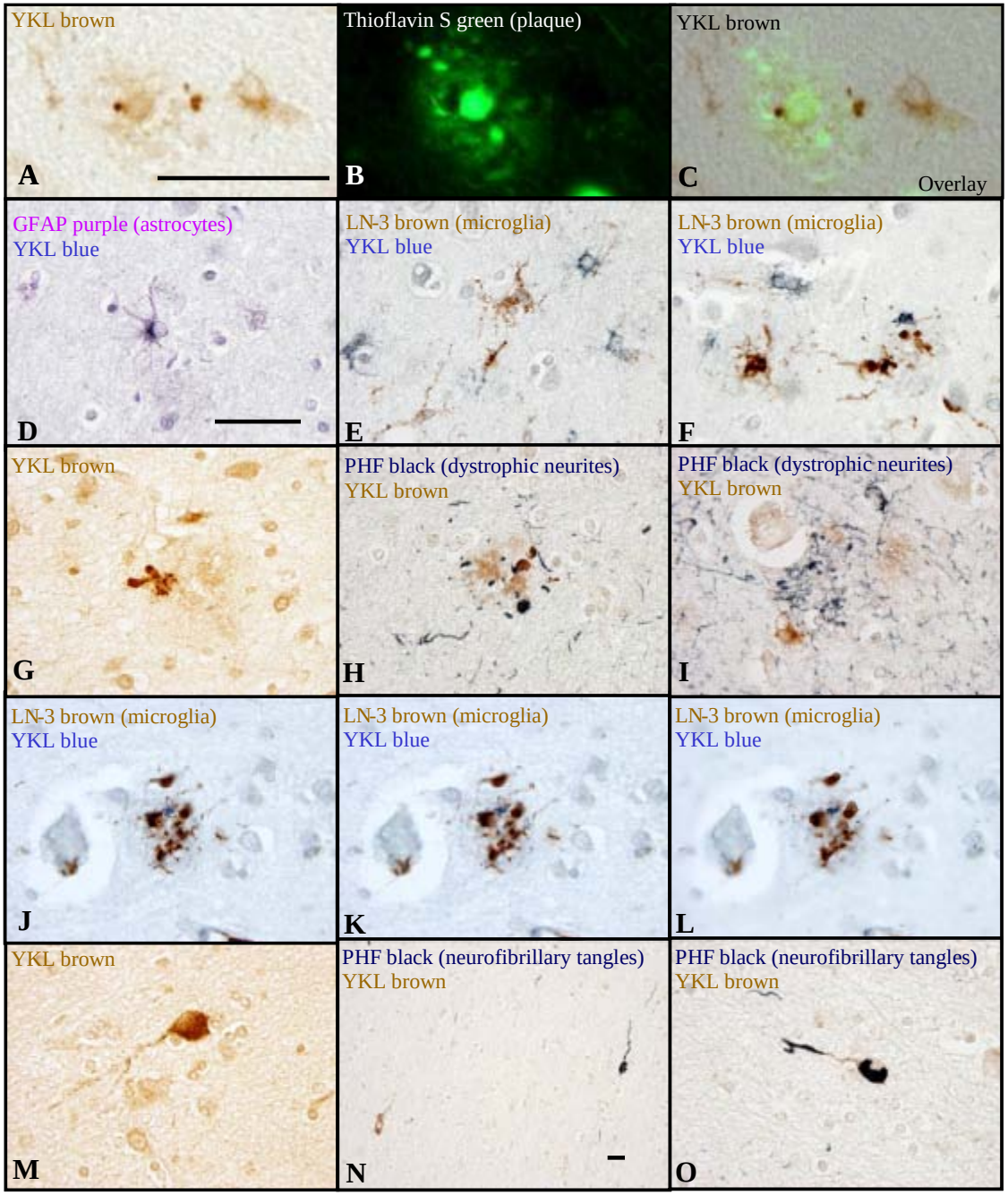
2D gel electrophoresis

↓

Fluorescence image analysis
Excise differentially expressed spots
Digest, sequence with MS

↳ Compare levels in AD vs controls in Discovery and Validation cohorts





YKL40

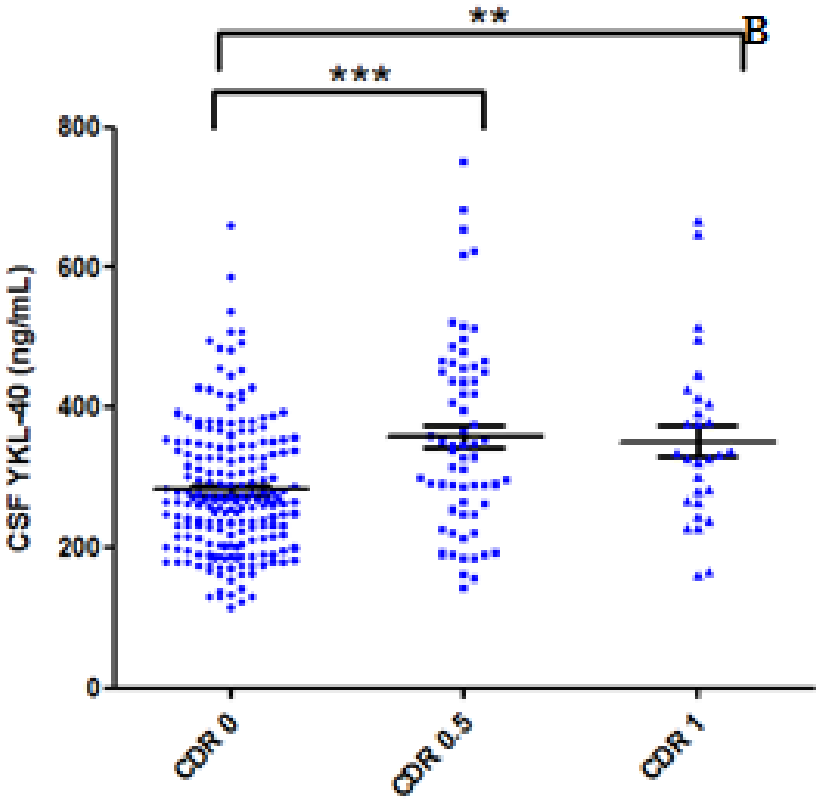
A secreted 40 kD glycoprotein

In AD, YKL i.r. is in the vicinity of fibrillar amyloid plaques **(A,B,C)**.

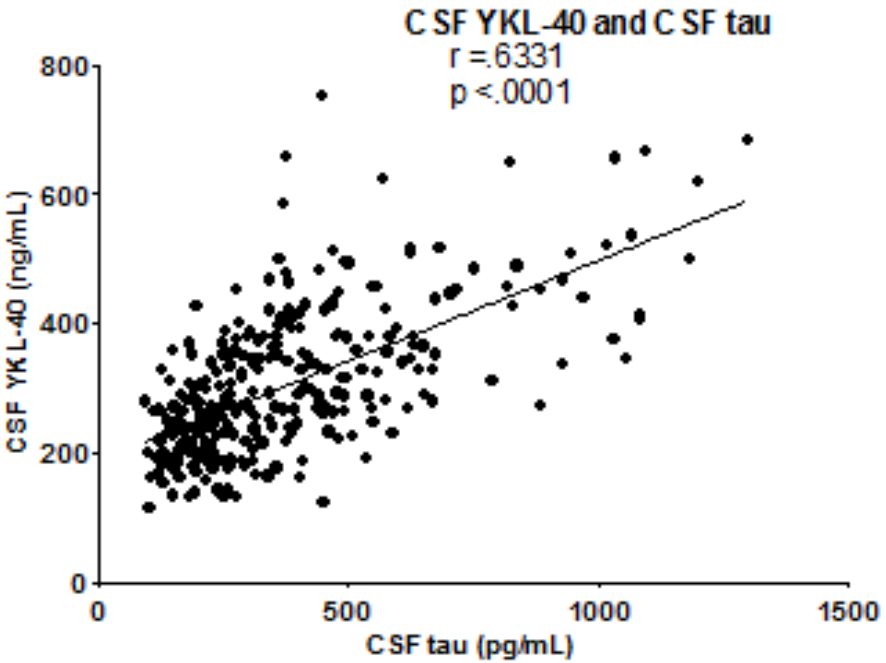
Present within a subset of GFAP-positive astrocytes **(D)** and not in LN-3-positive microglia **(E,F)**.

YKL-40 is also seen in swollen cell processes associated with plaques **(G)**; these lack reactivity for dystrophic neurite marker PHF-1 **(H,I)** and microglial marker LN-3 (**J,K,L**), and may represent astrocytic processes.

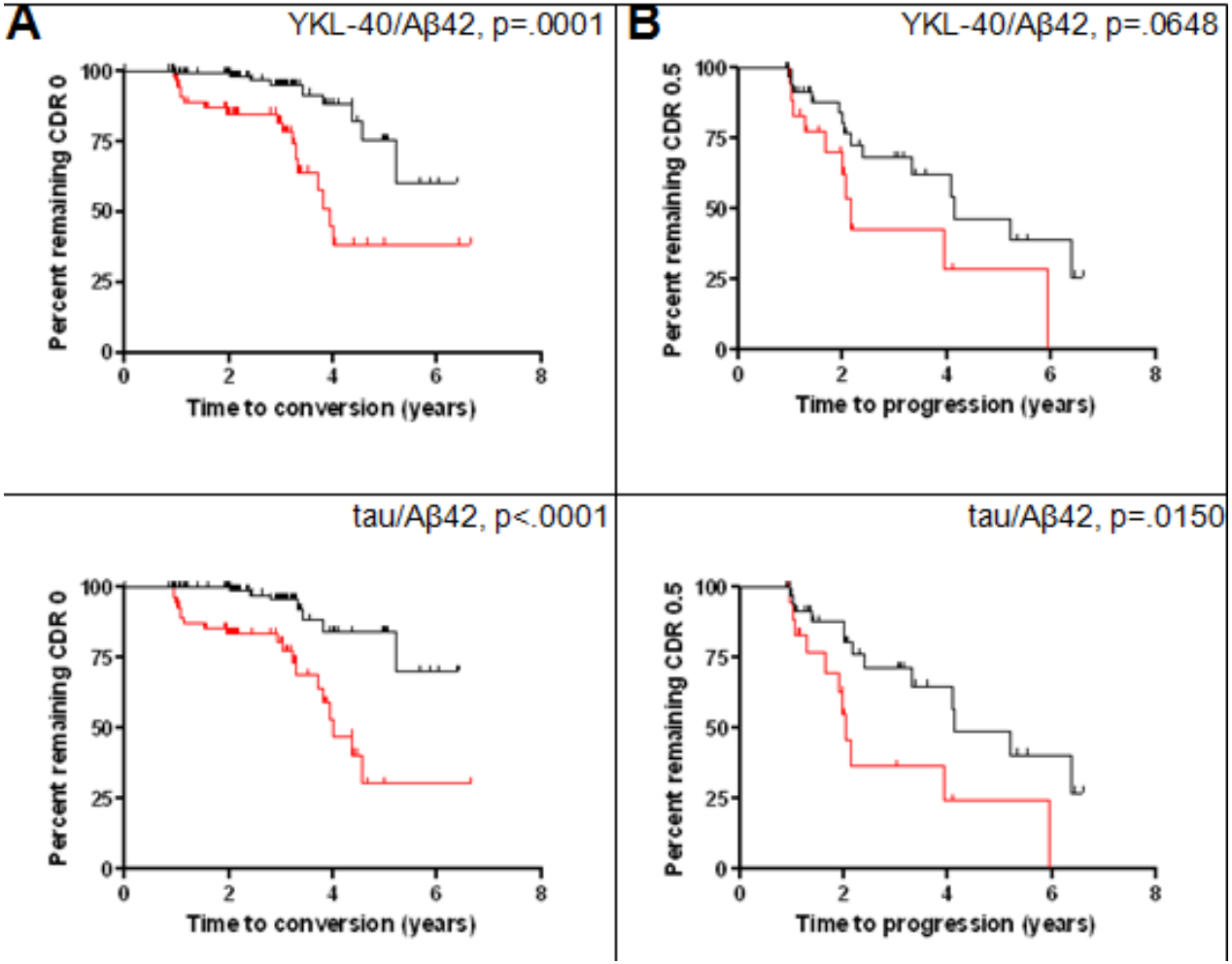
YKL-40 i.r. is also observed in occasional neurons in the superficial white matter **(M,N,O)**, some of which contain neurofibrillary tangles.



YKL40 levels were increased in CDR 1 vs 0 subjects in the discovery cohort, and in a larger independent sample in CDR 0.5 and 1



YKL40 levels correlated with tau and P-tau181levels



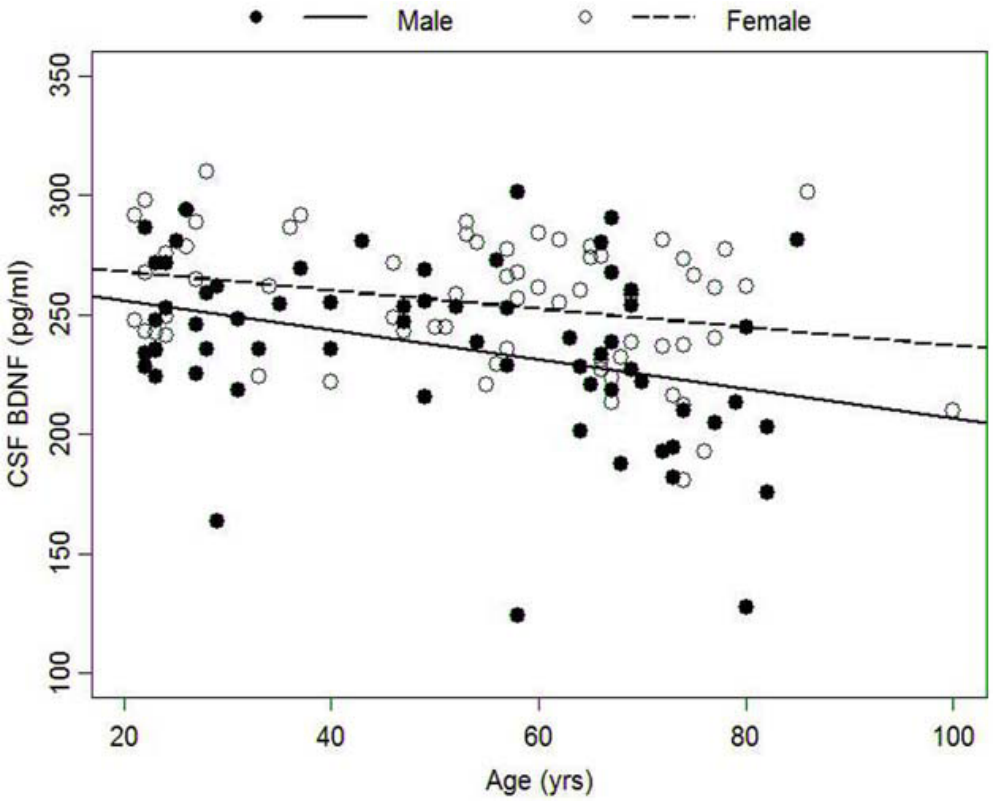
CSF YKL-40/Aβ42 and tau/Aβ42 as predictors of
A. conversion from CDR 0 to CDR>0 and
B progression from CDR 0.5 to CDR>0.5.
Kaplan-Meier estimates of rates of conversion and progression are shown; red curves represent the upper tertile and black curves the lower two tertiles.

BDNF, aging and AD

- Identified in a proteomic CSF study using iTRAQ:

  ↓ in AD (Zhang et al, 2008)
- BDNF is an activity-dependent secreted protein
- Present at synapses; roles in synaptic plasticity, hippocampal neuronal circuits
- Can promote neurogenesis in dentate gyrus
- Enhances aspects of spatial memory in rodents
- BDNF knockout mouse shows impaired LTP
- An allelic variant (Val66Met) may be associated with poorer memory performance and smaller hippocampal volume in humans

CSF BDNF in aging and AD



CSF BDNF levels are decreased in AD vs controls
(202 ± 31 vs 242 ± 33 pg/mL)

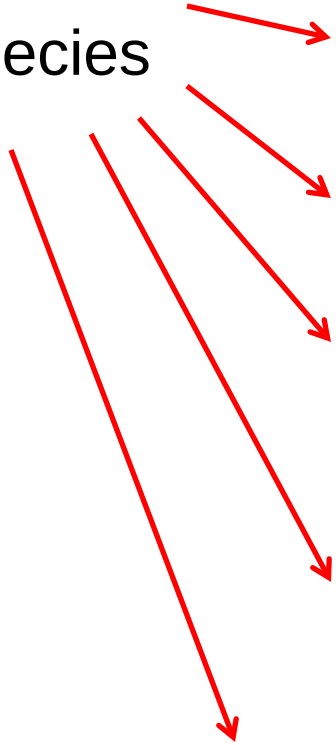
In NC, levels decrease with age
and
Lower BDNF was associated with worse performance and greater 12 month decline in immediate and delayed recall and category fluency.

Independent of APOE e4, and CSF Aβ42 and tau.

Li et al, 2009

Can CSF biomarkers help to map a cascade in AD?

Aβ toxic species



Parts of the cascade	**Potential biomarkers**
Damage to neurons and axons, tangle formation	Tau, P-tau neurofilaments
Glial reaction	GFAP, YKL40
Inflammation	S100b, cytokines
Oxidative stress	F2-isoprostanes
Synaptic damage	?
Synaptic function and plasticity	Neurotransmitters ? sAPPα, sAPPβ BDNF
Trafficking	SORLA /LR11
Lipids, cholesterol	24-OH-cholesterol
Neurogenesis	? BDNF

Thanks!!

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