The Role of Fluid Biomarkers in Preclinical Alzheimer's Treatment Trials

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Second Annual Early Alzheimer's Disease Workshop
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Trials Unit

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Outline

- "Re"-Defining AD and the implications for clinical trials
- Role of biomarkers
- CSF biomarkers in AD
- Potential use of CSF markers in AD prevention trials
- Benefits and current challenges

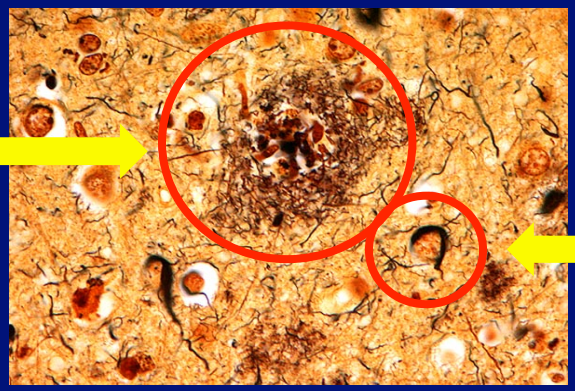
"Re"-Defining Alzheimer's Disease

- Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that culminates in end-organ (brain) failure which manifests as dementia.

...thus, AD refers to the neurodegenerative brain disorder

<u>regardless of clinical status</u>

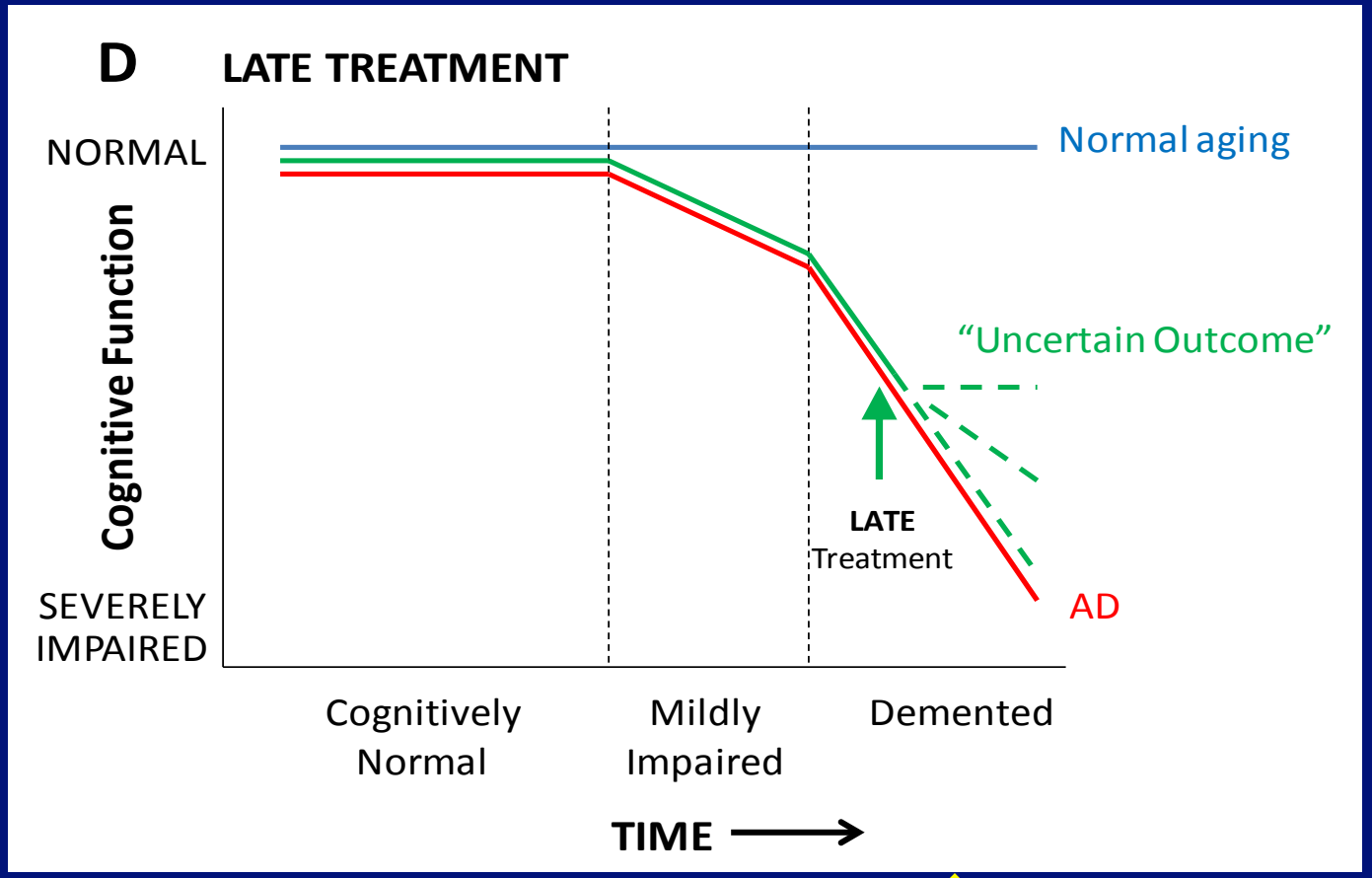
Amyloid plaques (amyloid-β)



Neurofibrillary Tangles (tau)

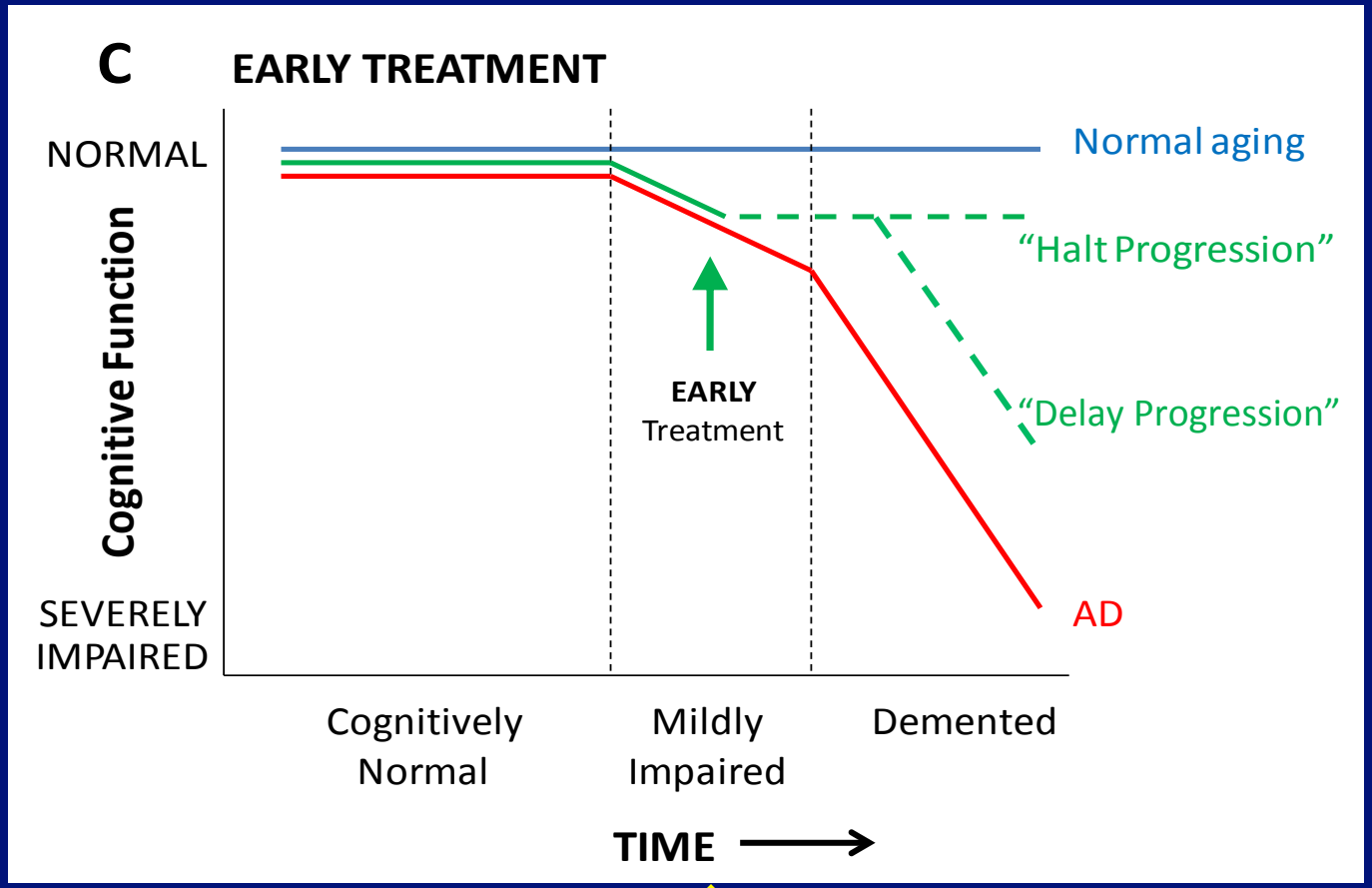
- AD can be conceptualized as having two major stages:
  1) Preclinical (pre-symptomatic)
  2) Symptomatic
     - Prodromal (incipient/MCI)
     - Dementia of the Alzheimer type

Late treatment…uncertain effect on dementia



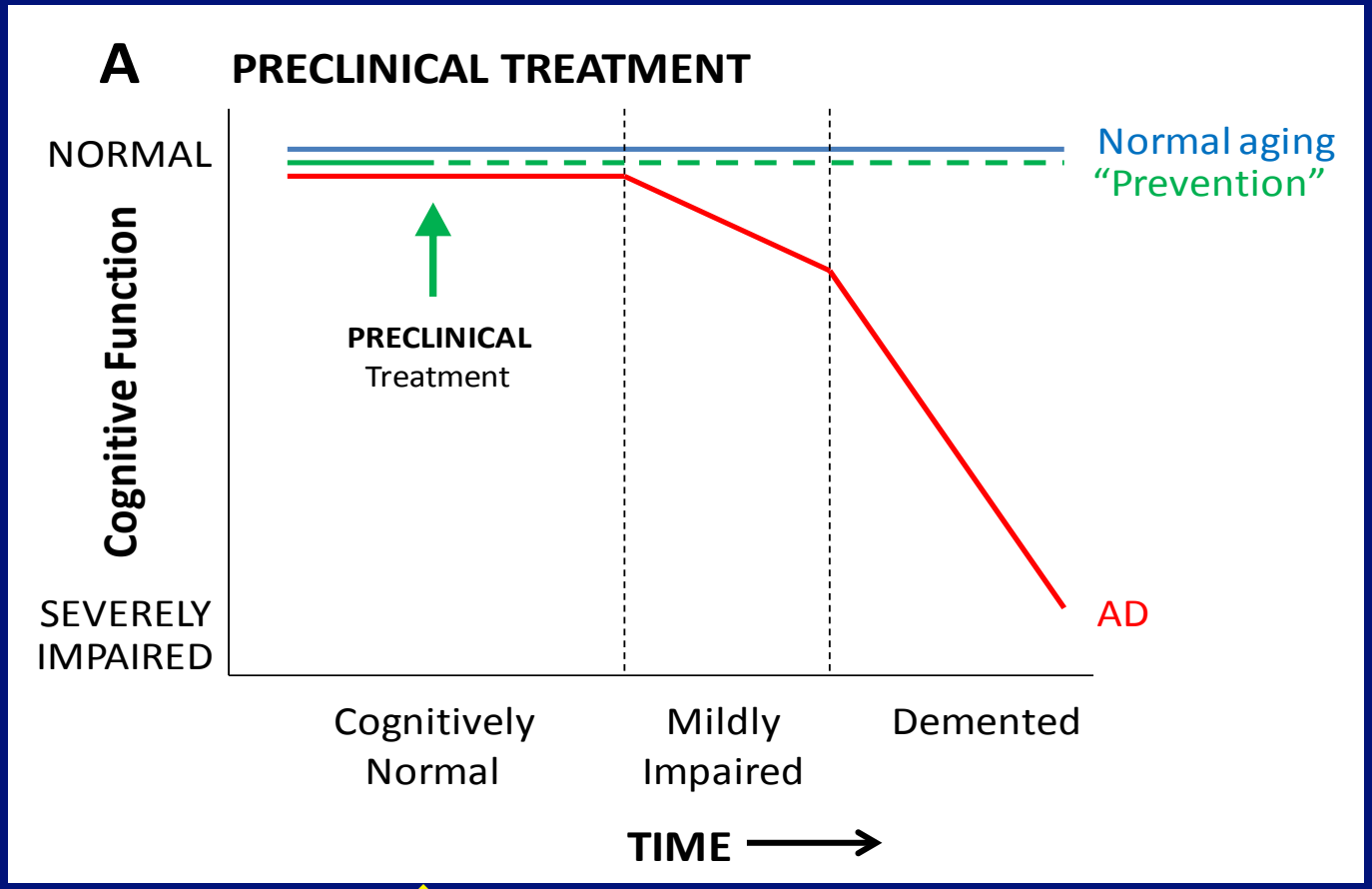
Demented

Early treatment…halt or delay established cognitive decline



Mildly impaired

Preclinical treatment…prevent cognitive decline



PREVENT

Cognitively normal

Potential uses of biomarkers in AD clinical trials

BM USE	GOAL	PRACTICALITY	EXAMPLES
Diagnostic	Ensure AD pathology in subjects	Reduce subject number and heterogeneity	Amyloid: CSF $A\beta_{42}$; amyloid PET Tangles/ neurodegeneration: CSF tau, ptau, VILIP-1; sMRI
Prognostic	Define disease stage	Reduce trial duration	Proximity to clinical impairment: CSF tau/$A\beta_{42}$, combination of CSF and sMRI
Theragnostic	Prove target engagement	Drug choice	Secretase inhibitor: CSF $A\beta$ Anti-amyloid: CSF $A\beta_{42}$, amyloid PET Tau kinase inhibitor: CSF ptau
Surrogate Outcome	Prove effect on downstream targets	Potentially reduce trial duration	Neurodysfunction/degeneration: CSF tau, VILIP-1; sMRI; fc-MRI

In sum, converging evidence demonstrates…

- There exists a "preclinical" stage of AD that likely spans ~10-15 years prior to dementia onset.
- The AD biomarker "signature" in CSF includes reductions in the level of $A\beta_{42}$ and increases in total tau and phosphorylated tau (p-tau).
- Changes in CSF measures are reflective of underlying disease pathologies (e.g., amyloid plaque load [amyloid imaging], neurodegeneration [MRI]).
- Certain biomarker changes can be detected in the preclinical (pre-symptomatic) stage (e.g., reduced $A\beta_{42}$, increased tau/$A\beta_{42}$).
- Presence of these pathologies and their biomarkers in the preclinical stage are not clinically benign, i.e., they are predictive of future cognitive decline.

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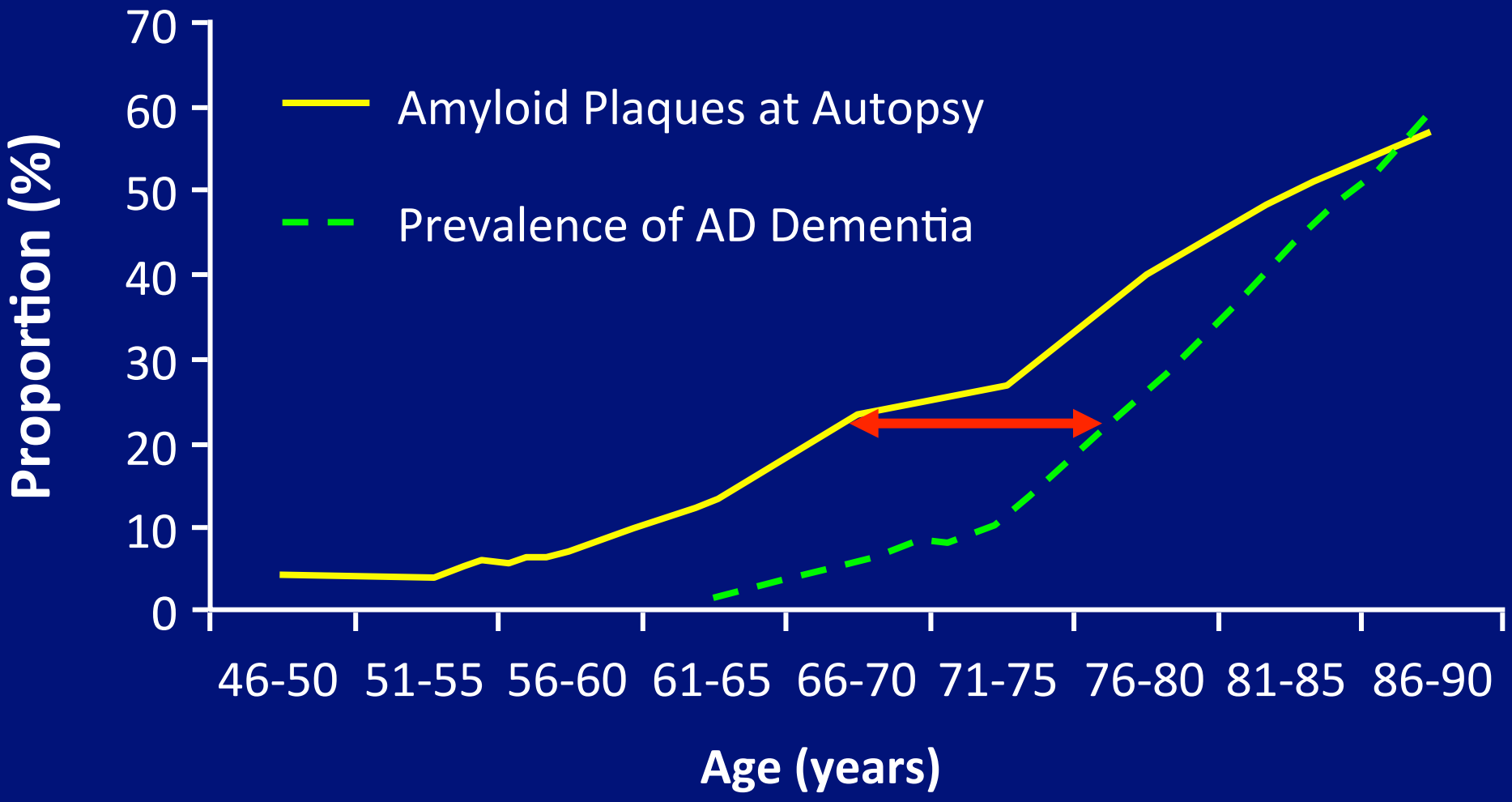
Prevalence of plaques compared to DAT suggests a "preclinical" stage of AD



DAT=dementia of the Alzheimer type

(Sperling et al., 2011, Alzheimers Dement 7:280-9
(figure courtesy of Drs. Mark Mintun and John Morris)

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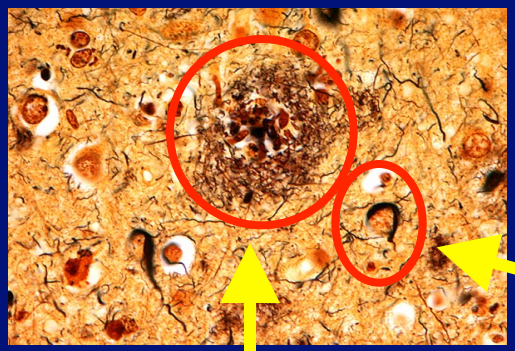
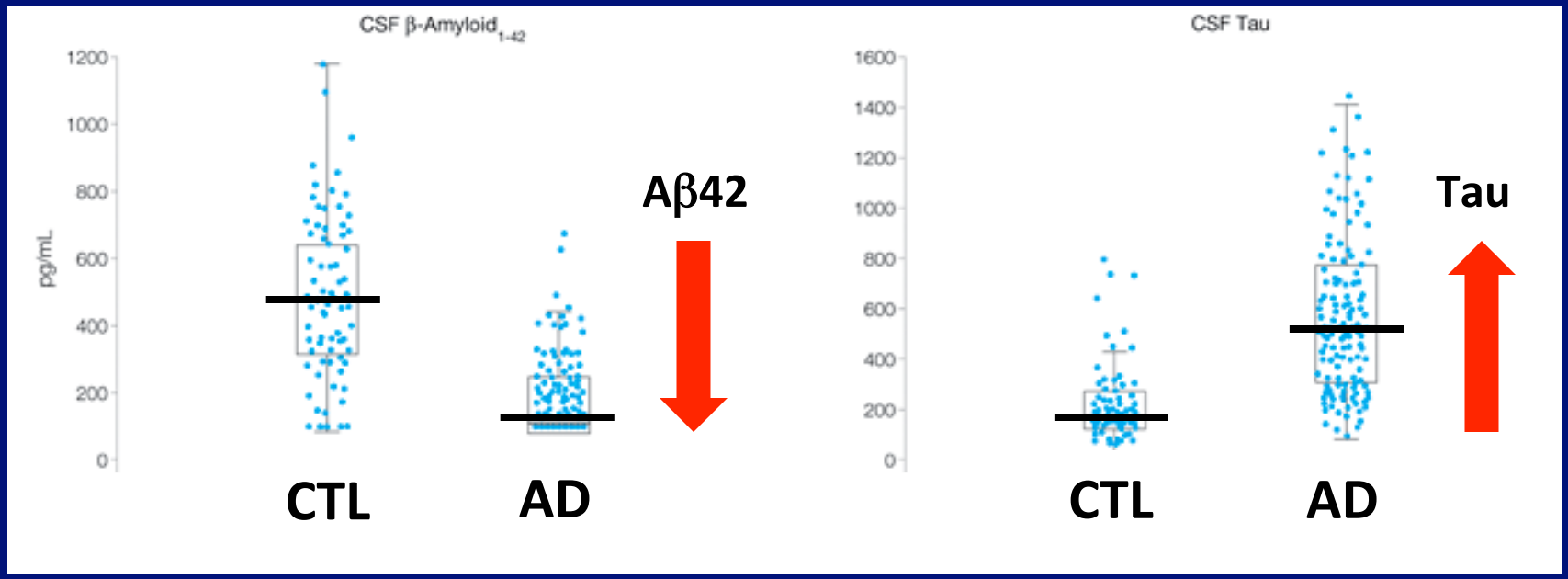
Established CSF biomarkers of AD





(Sunderland et al., 2003, JAMA 289:2094-103)

Published $A\beta_{42}$: sensitivity, 70-100%
specificity, 40-90%

Published Tau: sensitivity, 40-85%
specificity, 65-85%

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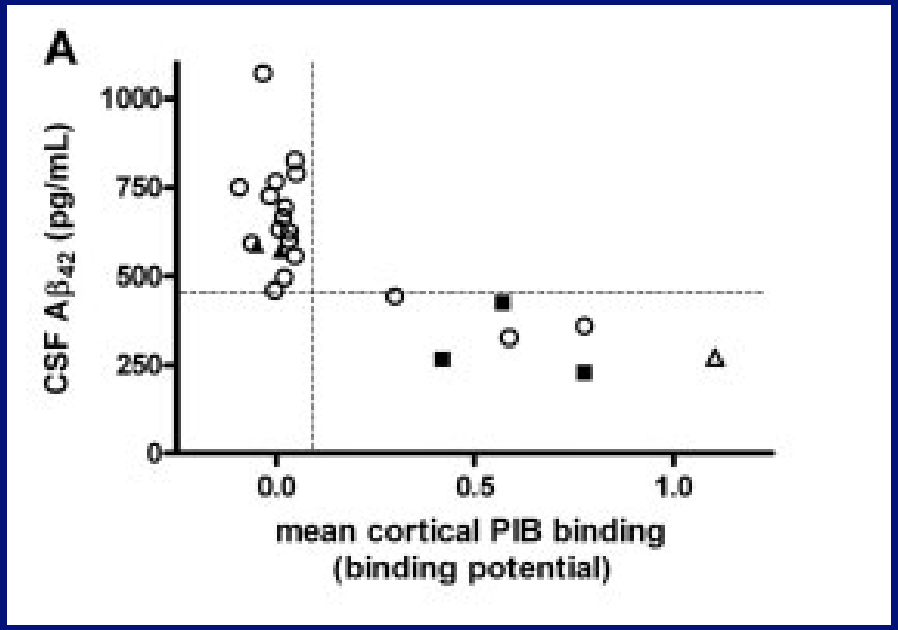
Low CSF $A\beta_{42}$ is a marker of cortical amyloid as detected by PET PIB, even in the absence of cognitive symptoms (CDR 0)

Mixed Cognitive States

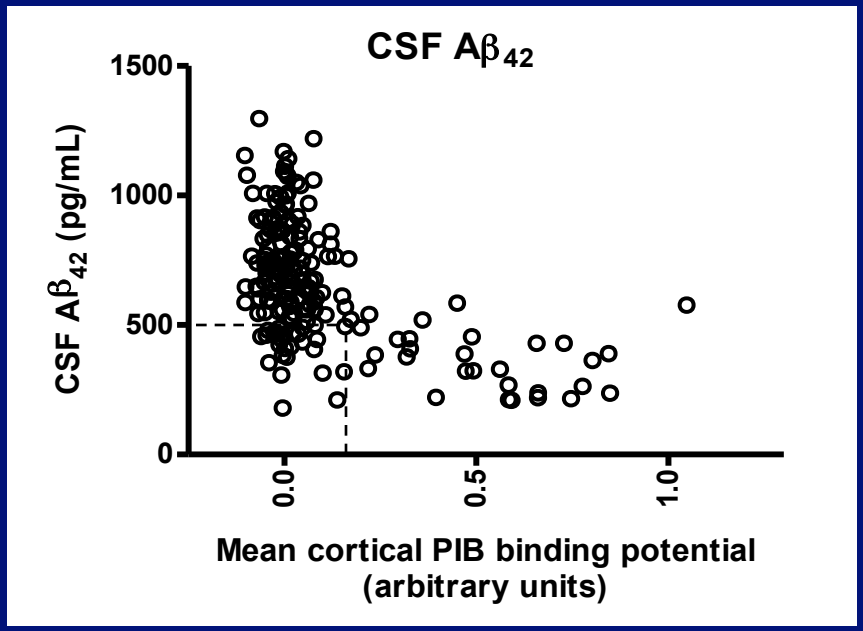


○ CDR 0 (cognitively normal)

Fagan et al., 2006, Ann Neurol 59:512-19

Forsberg et al., 2008, Neurobiol Aging, 29:1456-65
Grimmer et al., 2009, Biol Psychiatry, 65:927-34
Jagust et al., 2009, Neurology 73:1193-99
Tolboom et al., 2009, J Nucl Med, 50:1464-70
Forsberg et al., 2010, Curr Alz Res, 7:56-66

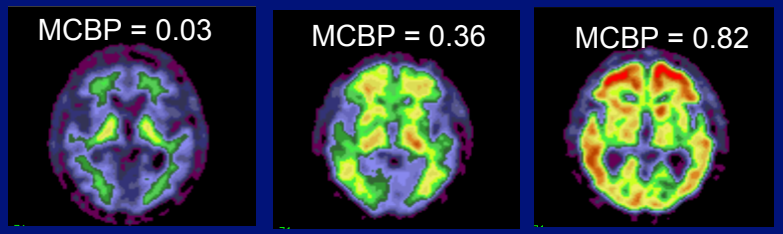
Cognitively Normal (CDR 0)



N=189 CDR 0

Mean age 64 years

Fagan et al., 2009, EMBO Mol Med 1:317-80



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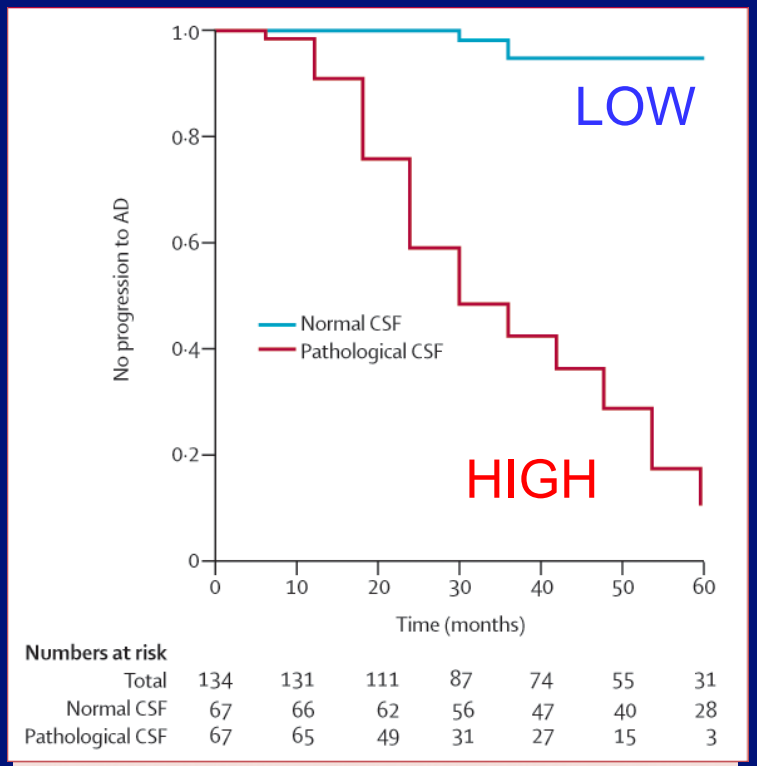
- Presence of these pathologies and their biomarkers in the <u>preclinical</u> stage are not clinically benign, i.e., they are predictive of future cognitive decline.

The CSF tau/Aβ_{42} ratio predicts progression from MCI to AD, as well as from cognitively normal to MCI or AD

MCI → AD



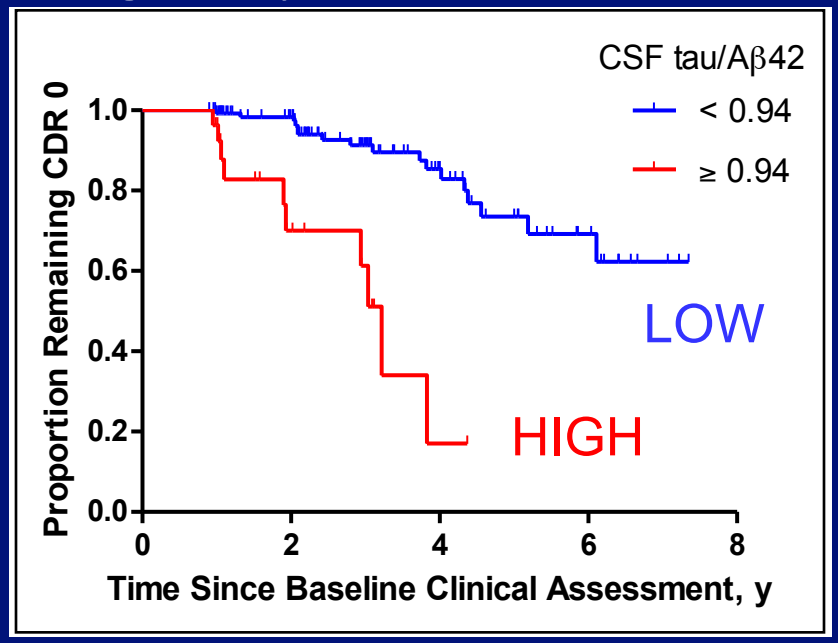
Numbers at risk							
Total	134	131	111	87	74	55	31
Normal CSF	67	66	62	56	47	40	28
Pathological CSF	67	65	49	31	27	15	3

	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Pathological CSF (T-tau and Aβ42)	30·0 (9·32–96·8)†	17·7 (5·33–58·9)†
Pathological CSF (P-tau$_{181}$ and Aβ42)	26·3 (8·16–84·5)†	16·8 (5·02–56·5)†

N=134 MCI

Hansson et al., 2006, Lancet Neurol 5:228-234

Cognitively normal → MCI/AD



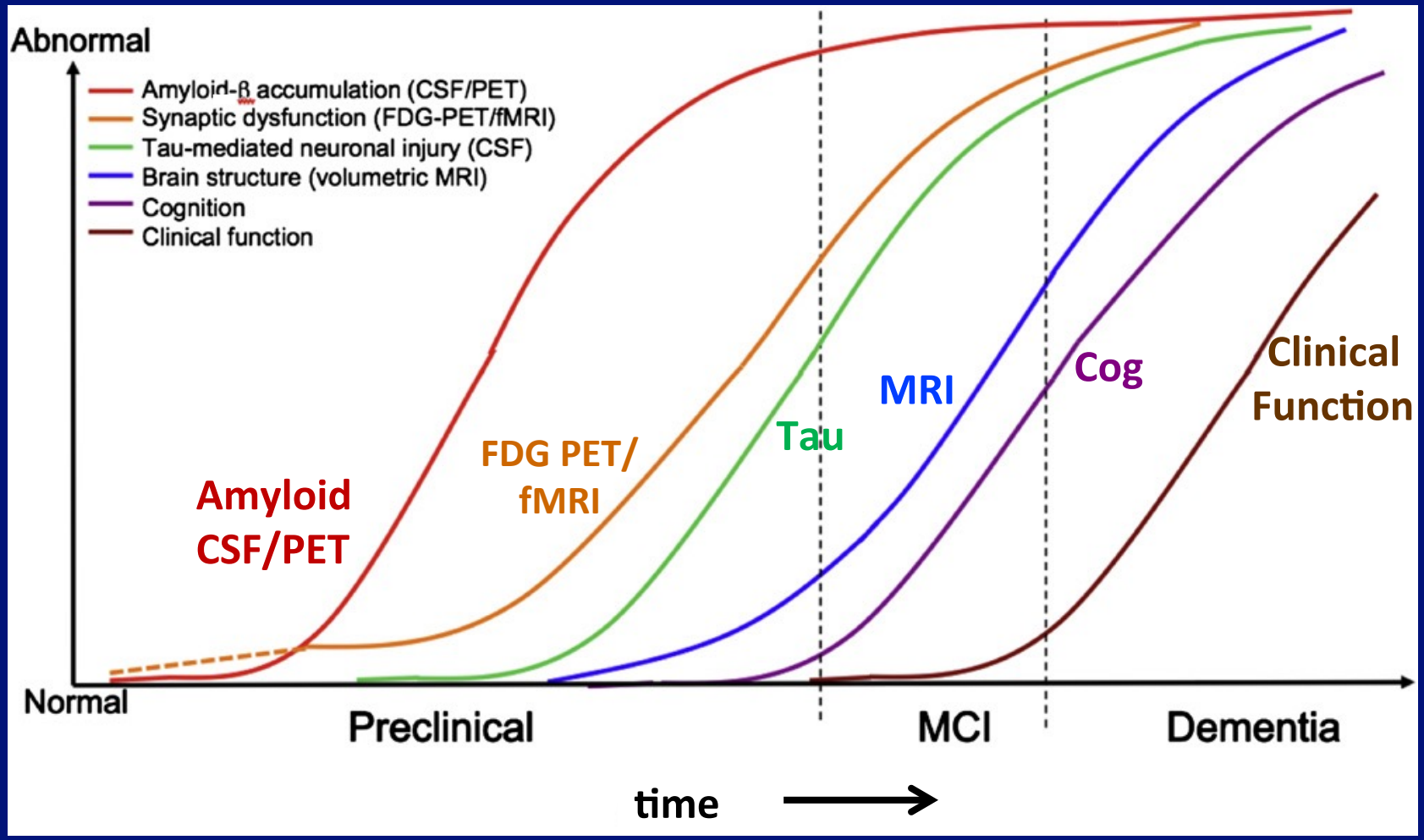
Upper 15% vs. lower 85% of values

(HR 9.82; 95% CI: 3.16-21.28, p<0.0001)

N=164 CDR 0, mean age 75 years at entry

Tarawneh et al., 2011, Ann Neurol, 70:274-85
Craig-Schapiro et al., 2010, Biol Psychiatry, 68:903-12
Fagan et al., 2007, Arch Neurol, 64:343-49
Li et al., 2007, Neurology, 69:631-39.

*Hypothetical model of dynamic biomarkers of AD**



*Derived from published cross-sectional analyses of LOAD

Sperling et al., 2011, Alzheimers Dement 7:280-92
(Modified from Jack et al., 2009, Brain 132:1355-65)

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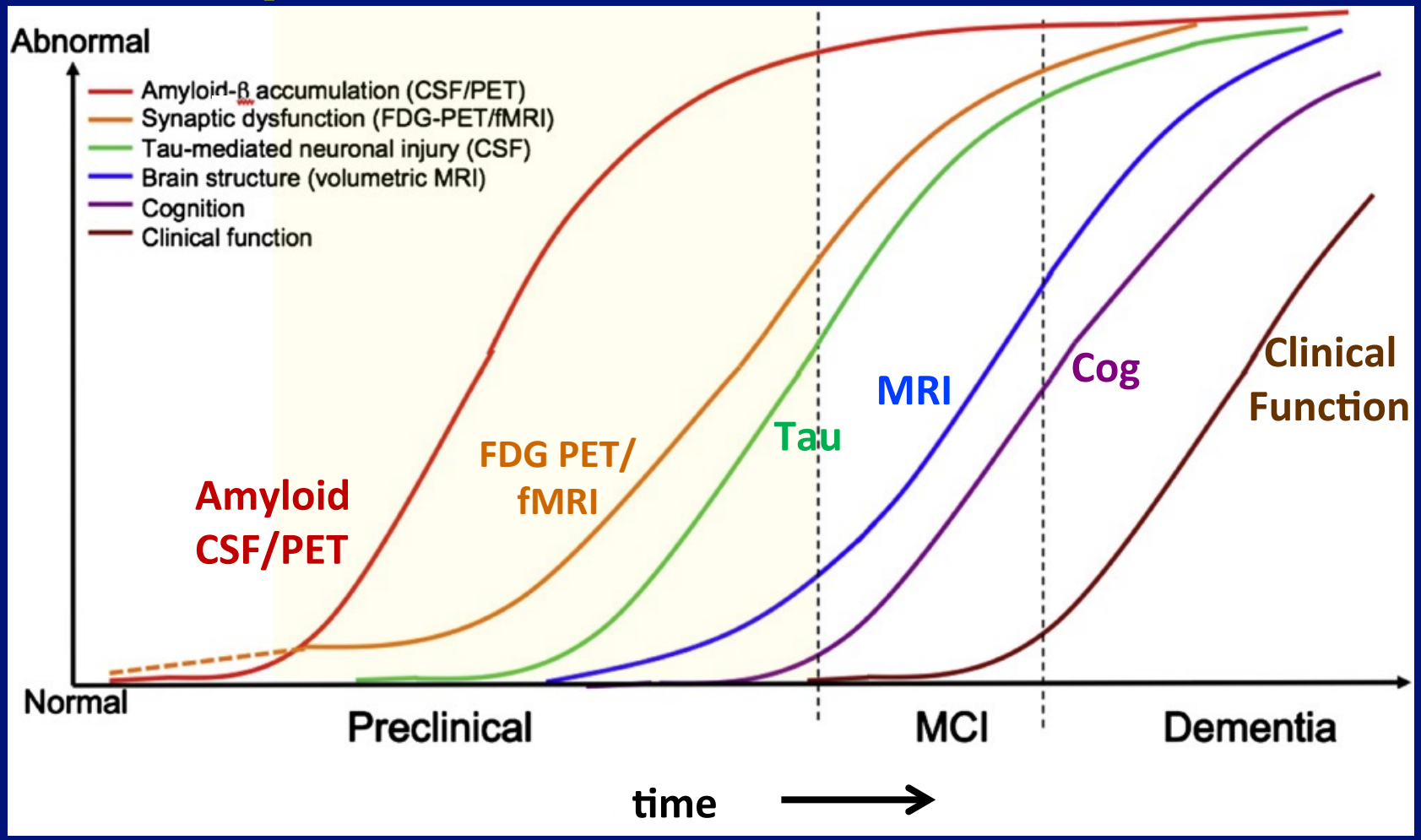

*Derived from published cross-sectional analyses of LOAD

Sperling et al., 2011, Alzheimers Dement 7:280-92
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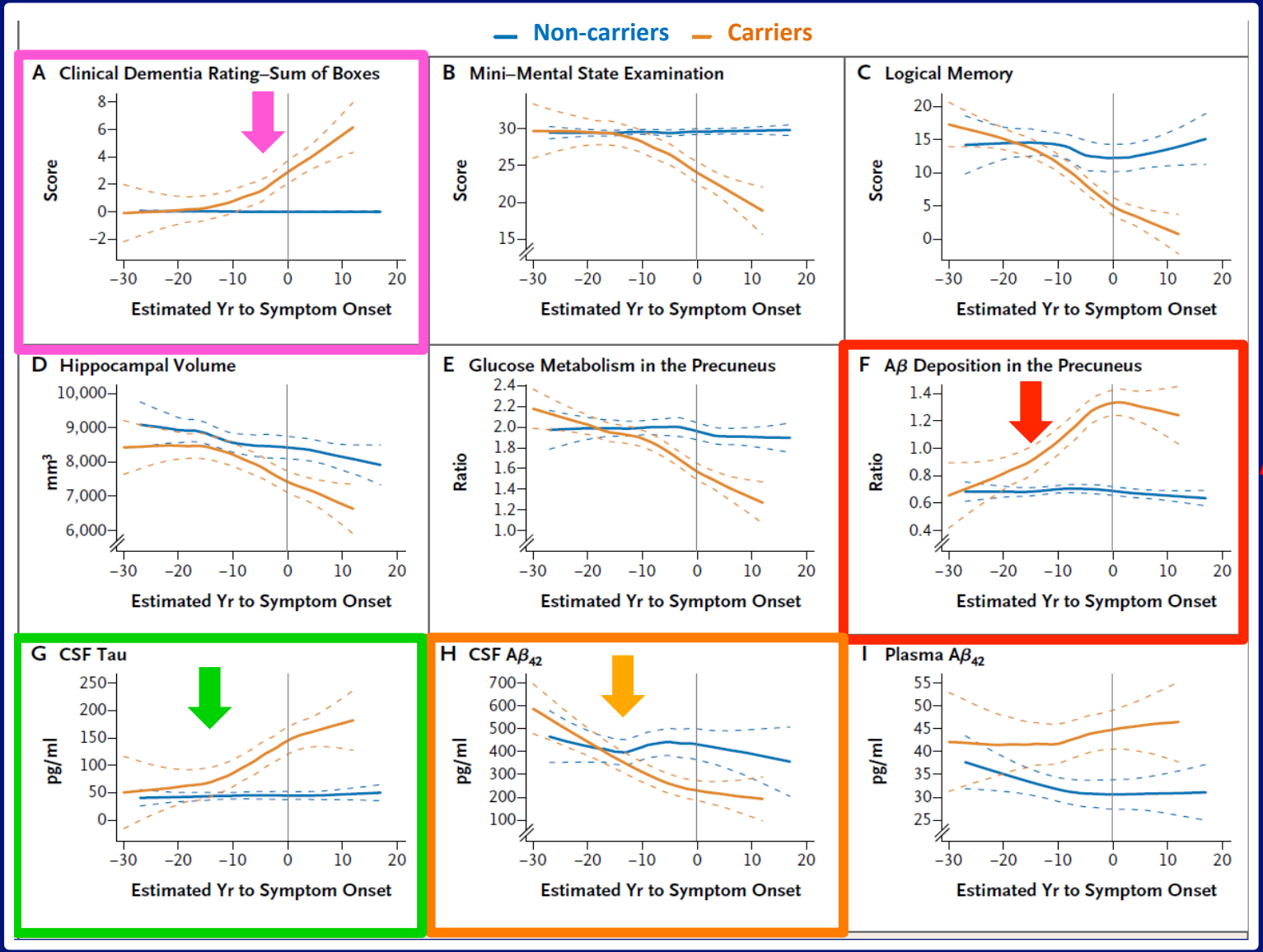
Estimated trajectories of cognitive and biomarker changes in the DIAN observational study

CDR-SB



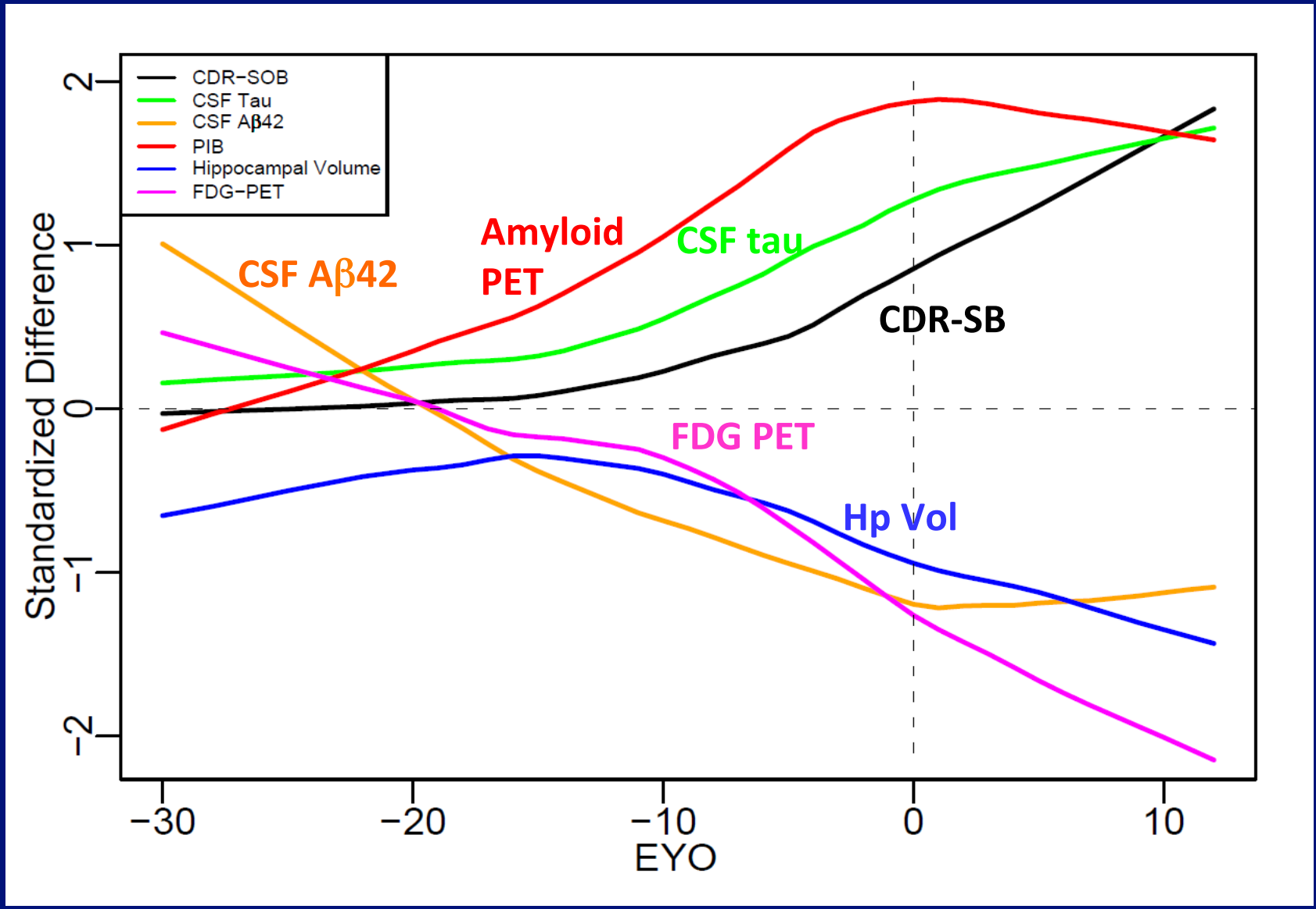
Amyloid PET

CSF tau

CSF Aβ42

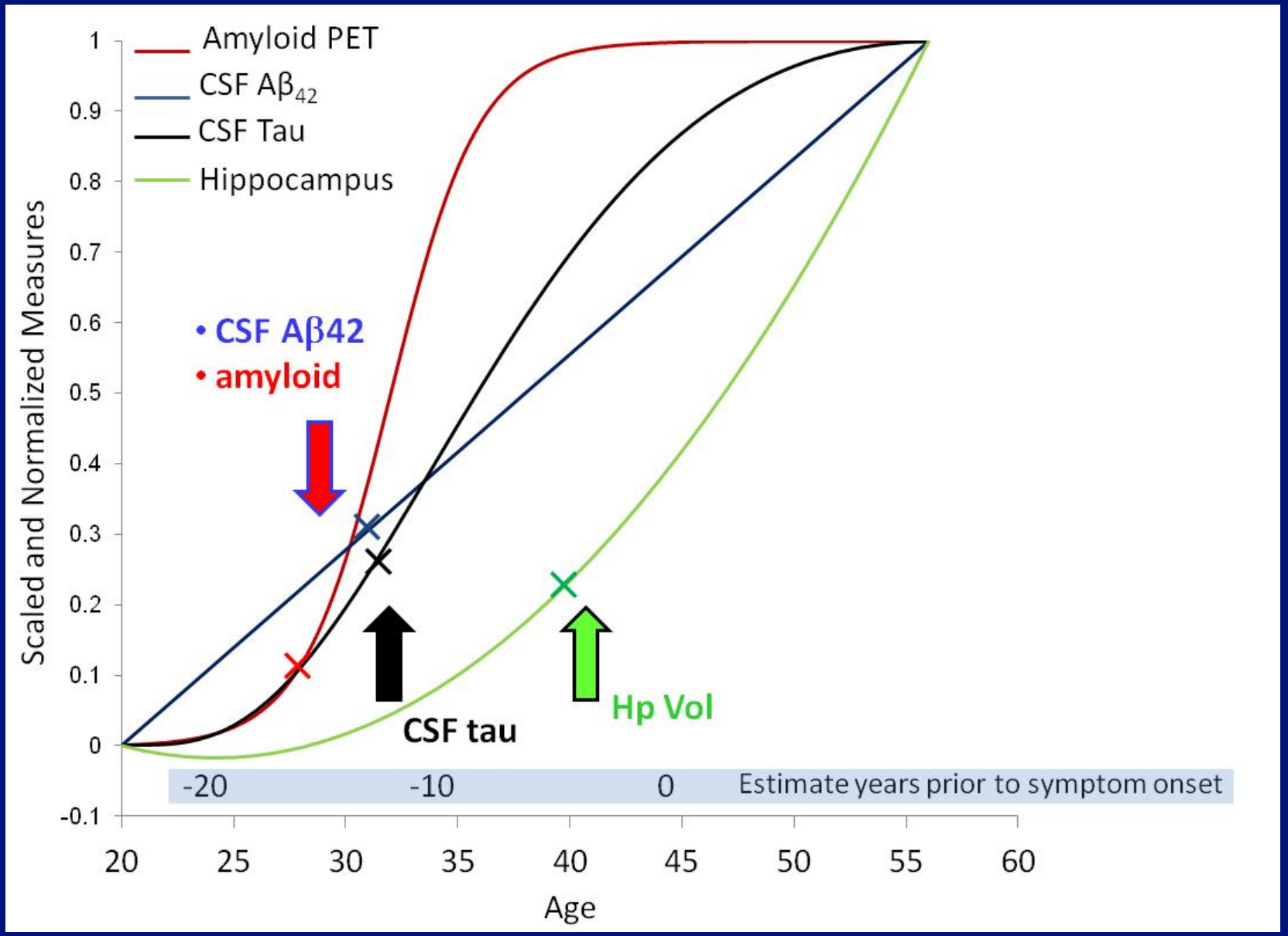
(Bateman et al., NEJM, 2012)

Biomarker curves in the DIAN observational study



(Bateman et al., NEJM, 2012)

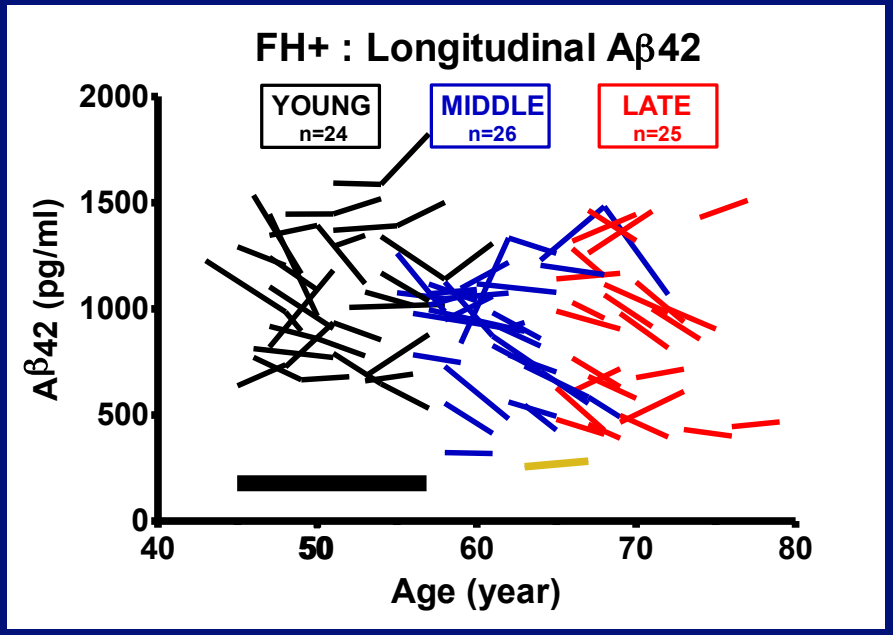
Biomarker curves in the API observational study



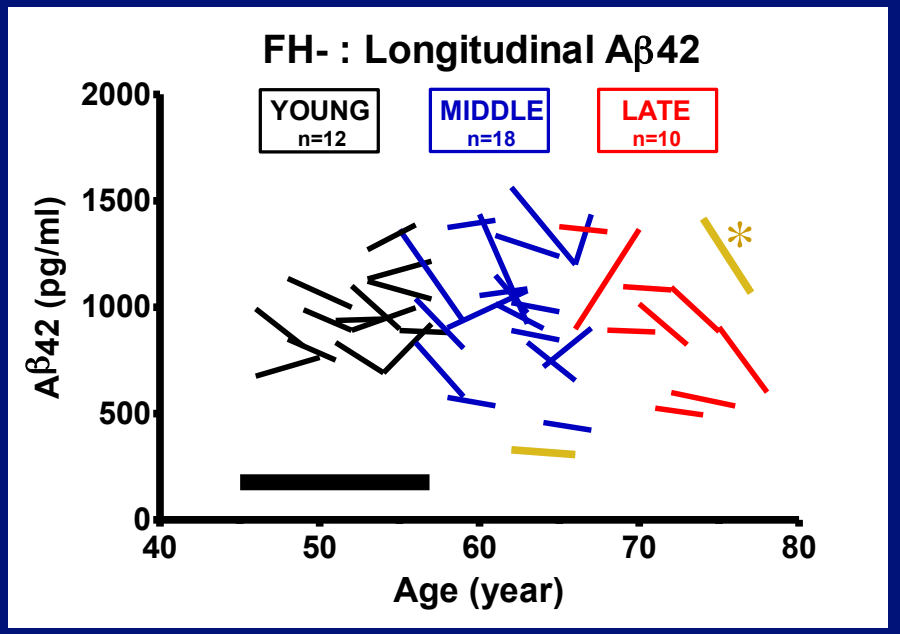
(figure courtesy of Fleisher et al., AAIC 2012)

Longitudinal change in levels of CSF Aβ42 within individuals in the longitudinal Adult Children Study

FH+



FH-



CSF Aβ42 begins to decrease during early middle-age (45-54 yrs) in more individuals with a positive FH compared to those with a negative FH, and levels continue to drop with age, even in the FH- group.

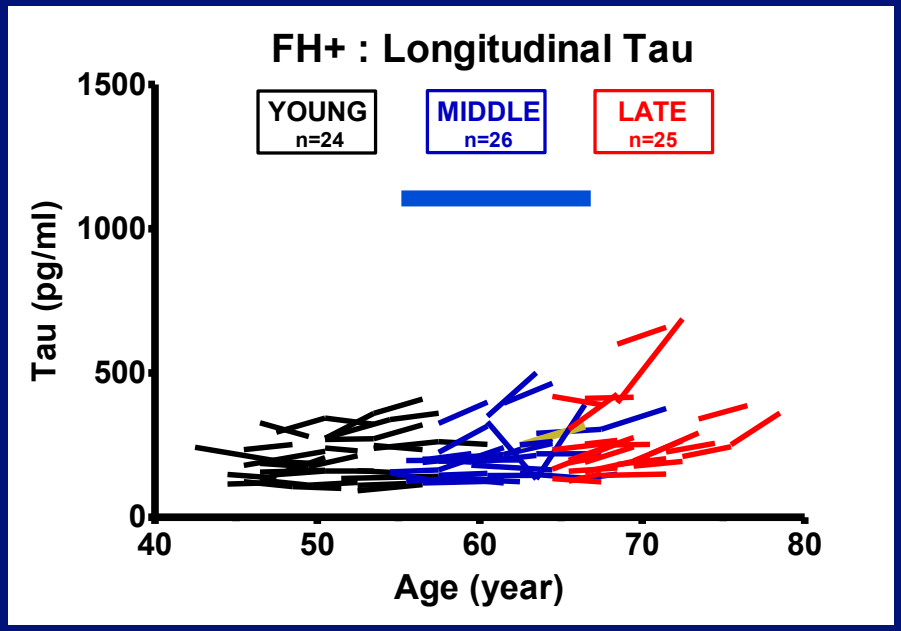
* Gold; progressed to CDR>0

(ACS participants are CDR 0 at study enrollment)

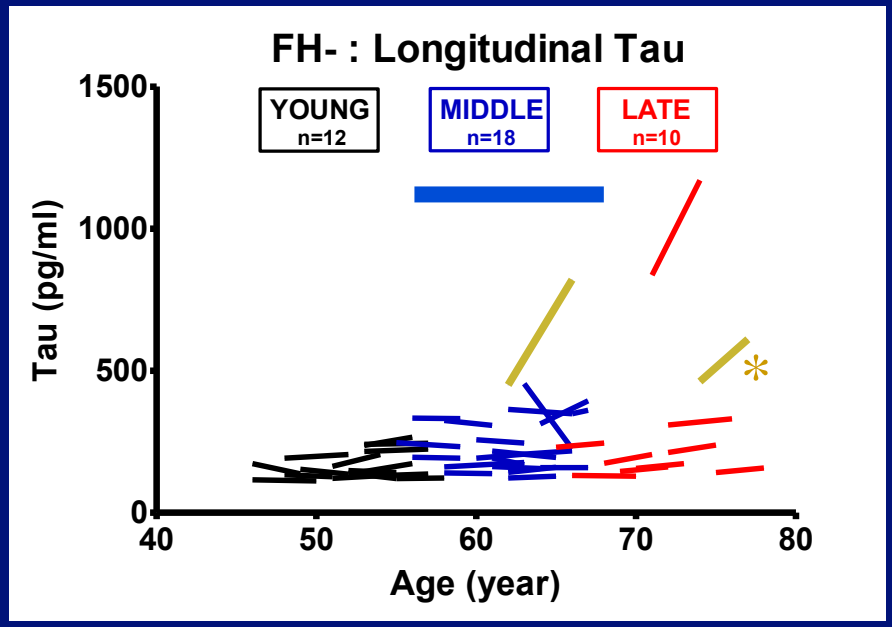
(Fagan et al., unpublished)

Longitudinal change in levels of CSF tau within individuals in the longitudinal Adult Children Study

FH+



FH-



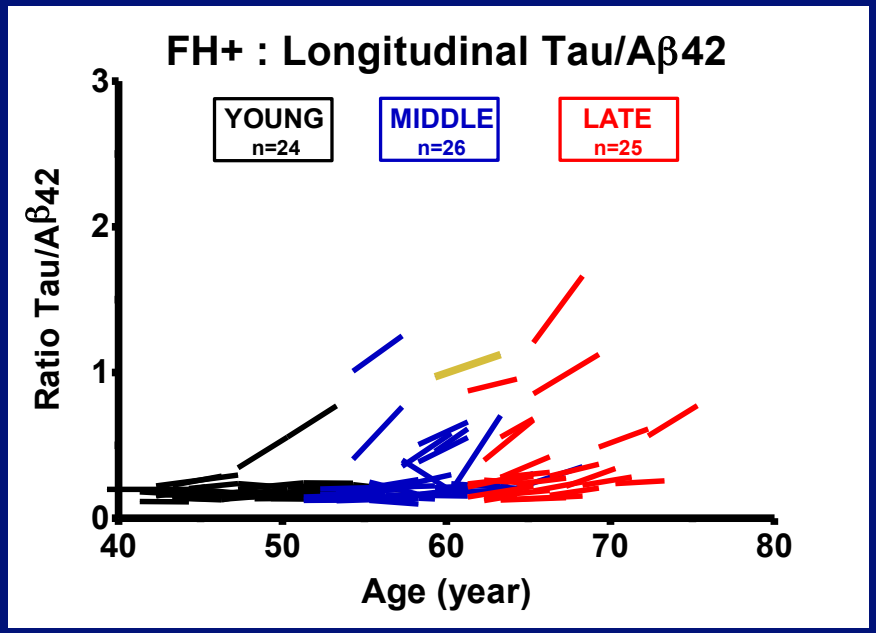
CSF tau begins to increase during mid- middle age (55-64 yrs) in more individuals with a positive FH compared to those with a negative FH. Levels continue to rise with age (late middle-age, 65-74 yrs), even in some individuals in the FH- group.

(Fagan et al., unpublished)

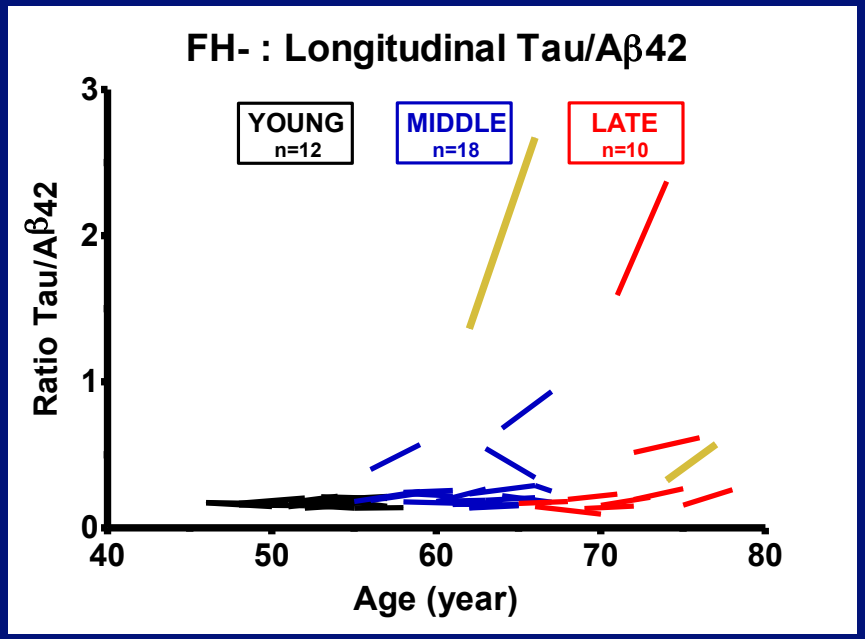
* Gold; progressed to CDR>0

Estimated annual rate of change in the CSF tau/Aβ42 ratio in the longitudinal Adult Children study

FH+



FH-

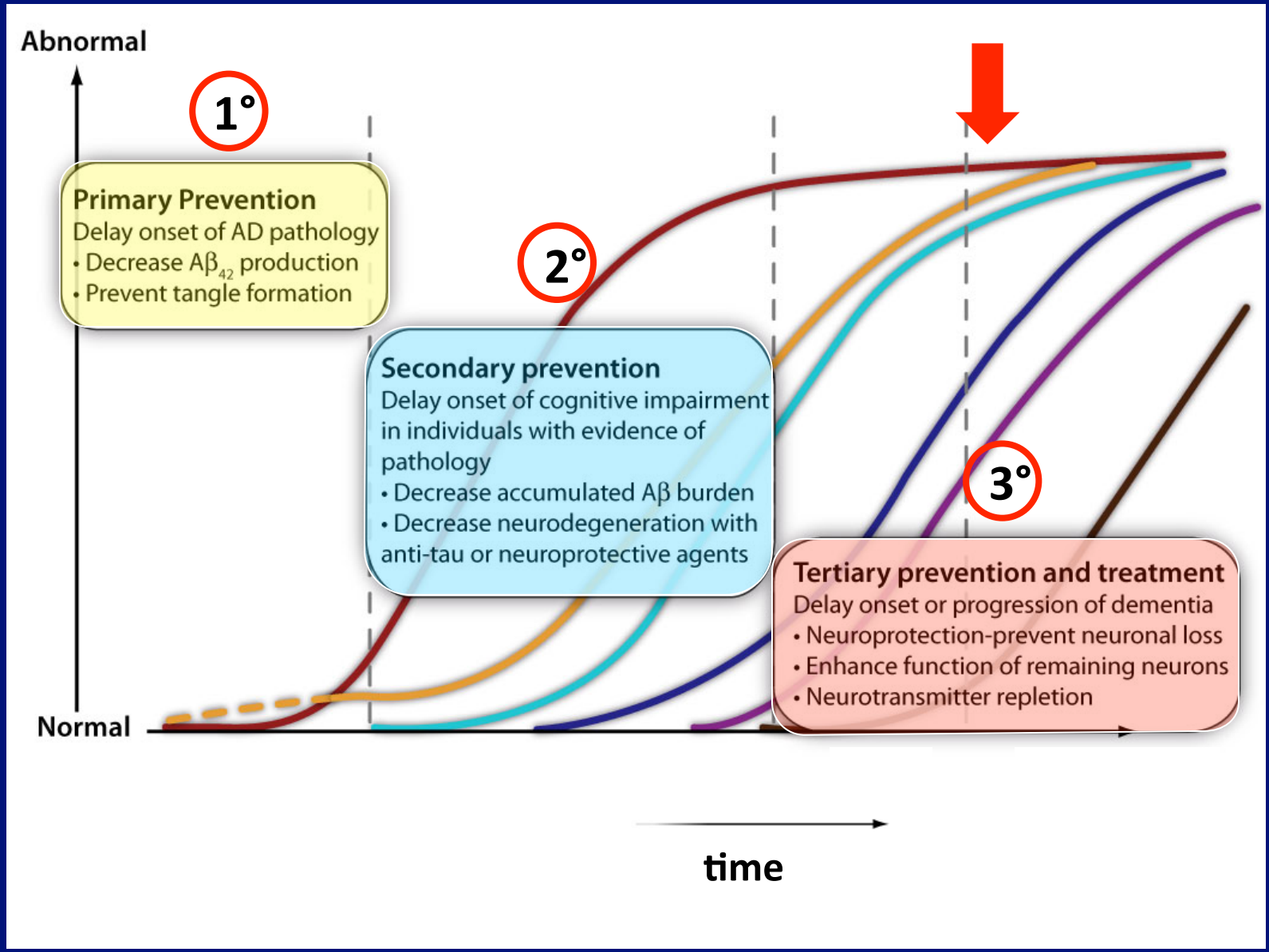


The CSF tau/Aβ42 ratio increases with age, starting in mid middle-age, in both FH groups. Increases are observed more in the FH+ group compared to the FH- group.

(Fagan et al., unpublished)

* Gold; progressed to CDR>0

Proposed stages of AD with potential prevention and treatment targets



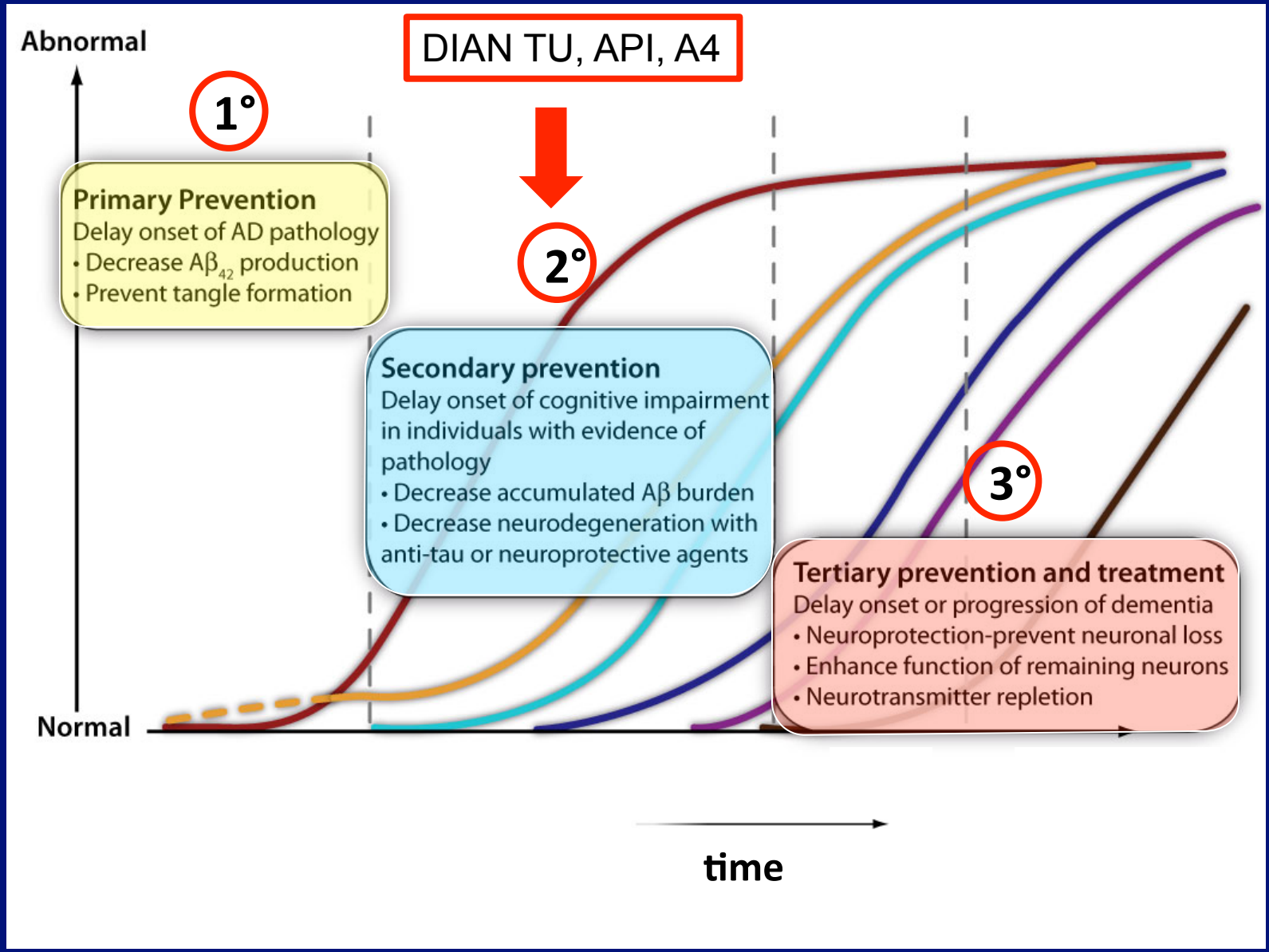
(Adapted from Sperling et al., 2011, Sci Transl Med 3:111cm33-111cm33)

Examples of CSF outcomes in clinical trials of symptomatic AD

- AN1792: ↓CSF tau but no change in Aβ42 in antibody responders
  (Gilman et al., 2005, Neurology 64:1553-62)
- Scyllo-inositol: ↓CSF Aβ42 but no difference in tau or p-tau
  (Salloway et al., 2011, Neurology 77:1253-62)
- Avagasestat (Phase 2): ↓CSF Aβ42 at highest dose only
  (Coric et al., 2012, Arch Neurol, 69:1430-40)
- Solanezumab (Phase 2): 12 weekly doses, dose-dependent ↑ plasma and CSF total Aβ1-40 and Aβ1-42 (bound and unbound) and ↑ in unbound CSF Aβ1-42 *(Farlow et al., 2012, Alzheimer's & Dem 8:261-71)*
- Bapineuzumab (Phase 2): ↓CSF p-tau and trend for ↓tau but no difference in Aβ42 *(Blennow et al., 2012, Arch Neurol 69:1002-10)*
- Bapineuzumab (Phase 3): ↓CSF p-tau in *APOE4* carriers and in the 1 mg/kg dose in non-carriers, but no significant effect on Aβ42
  (Sperling and Salloway, 2012, EFNS)

(slide courtesy of Dr. Stephen Salloway)

Proposed stages of AD with potential prevention and treatment targets



(Adapted from Sperling et al., 2011, Sci Transl Med 3:111cm33-111cm33)

Proposed Study Design for the DIAN Trials Unit (DIAN TU)

DRUG	TYPE	BM OUTCOME (TARGET)	BM OUTCOME (DOWNSTREAM)	FLUID BM (EXPLORATORY)
Solanezumab (LILLY)	Anti-Aβ antibody	TBD	CSF tau, ptau181, sMRI	FDG PET, fcMRI
Gantenerumab (ROCHE)	Anti-Aβ antibody	TBD	CSF tau, ptau181, sMRI	FDG PET, fcMRI
TBD	TBD	TBD	TBD	TBD

- 2 yr treatment to **BM outcome** + 3 yr cognitive outcome for promising drug(s)
- DIAN and DIAN Expanded Registry, N=240 (mixed mutations) (ADAD)
- N=240 (160 MC, 3 drug arms + pooled placebo, 40 each; ~80 NC, placebo)
- Age = -15 to +10 years compared to parental age of dementia onset

DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit

Proposed Study Design for the Alzheimer Prevention Initiative (API)

DRUG	TYPE	BM OUTCOME (TARGET)	BM OUTCOME (DOWNSTREAM)	FLUID BM (EXPLORATORY)
Crenezumab (Genentech)	Anti-Aβ antibody	TBD	CSF tau, ptau181, sMRI, amyloid PET, FDG PET, fcMRI	TBD

- 5 yr treatment to **cognitive outcome** (with 2 yr interim BM and cognitive analysis)
- *PSEN1E280A* Colombian kindred (ADAD)
- N= ~300 (~100 MC + drug, ~100 MC + placebo, ~100 NC placebo)
- Age = 30-60 yrs in presymptomatic phase

ALZHEIMER'S PREVENTION INITIATIVE

Proposed Study Design for the Anti-Amyloid Treatment in Asymptomatic AD Trial (A4)

DRUG	TYPE	BM OUTCOME (TARGET)	BM OUTCOME (DOWNSTREAM) OR FLUID BM (EXPLORATORY)
TBD	TBD	TBD	CSF Aβ42, tau, ptau181, amyloid PET, sMRI, FDG PET, fcMRI

- 3 yr treatment to **cognitive outcome** (with 2 yr additional clinical follow-up)
- older cognitively normal individuals (LOAD)
- N= 1000 (500 amyloid PET-positive + drug, 500 amyloid PET-positive + placebo)
- Age ≥ 70yrs

A4

Benefits and current challenges of using fluid biomarkers in AD prevention trials

Benefits

- Able to identify the presence of AD pathologies in the absence of cognitive symptoms
- Able to evaluate therapeutic target engagement
- Able to stage disease pathology
- Able to track progression of disease pathology and evaluate potential therapy-related disease modification
- Can assess multiple analytes in a single sample
- Allows for better trial design (fewer subjects, shorter duration, lower cost) and assessment of effects on underlying disease pathologies

Current Challenges

- Current lack of protocol and assay standardization
- Sub-optimal assay reproducibility
- Difficult to define normal vs abnormal (cut-off values)
- Misperceptions regarding the safety, tolerability and utility of CSF collection and analysis
- Need for assay development and validity in the presence of the therapeutic agent (especially antibody-based therapies)
- Need to validate the relationship between biomarker change and cognitive outcome

Acknowledgments

The Knight Alzheimer's Disease Research Center at Washington University in St. Louis

Our study participants

DIAN TU
Dominantly Inherited Alzheimer Network Trials Unit

- DIAN Consortium

ALZHEIMER'S PREVENTION INITIATIVE

- Adam Fleisher
- Eric Reiman
- Jessica Langbaum

A4

- Reisa Sperling
- ADCS