CSF Predictors of Progression

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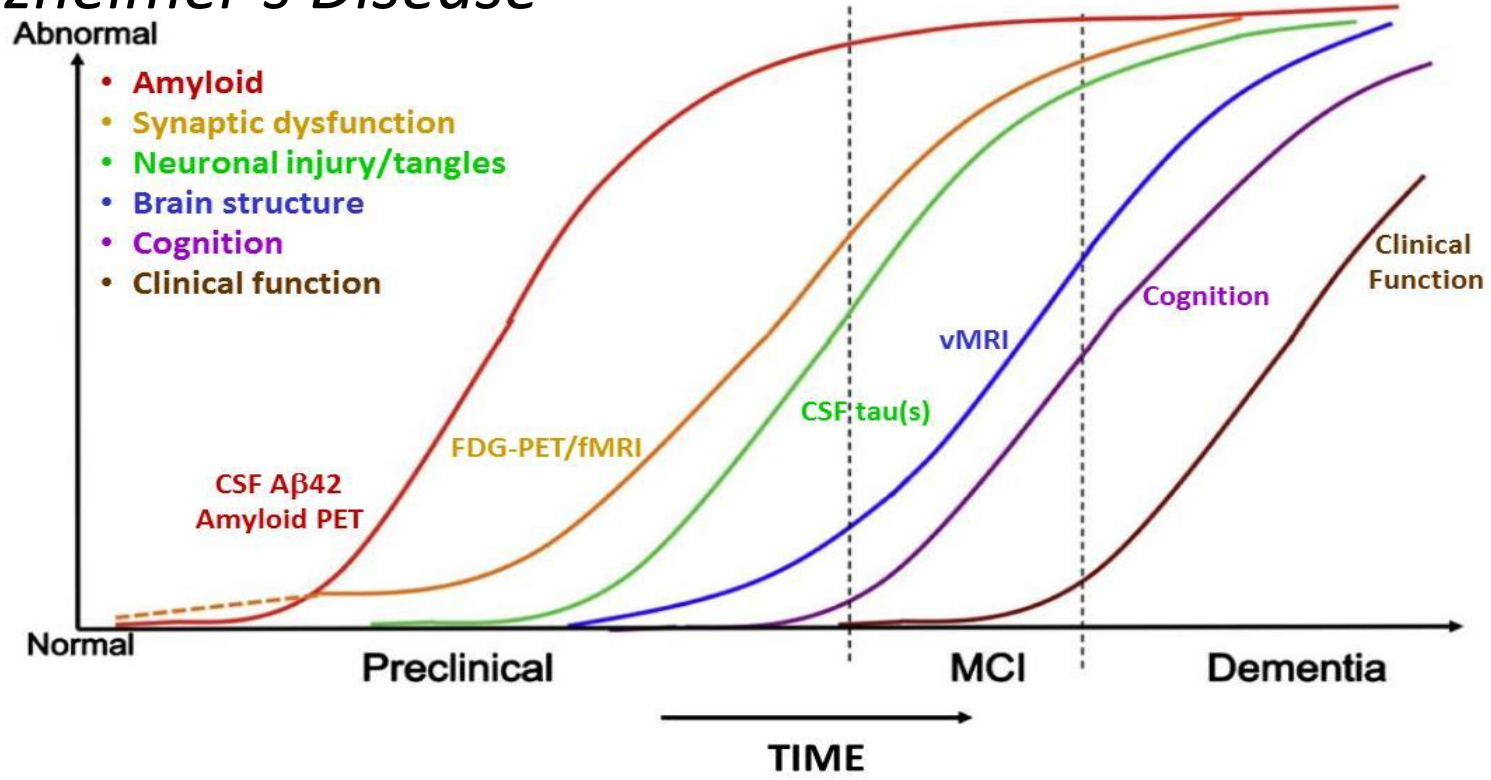
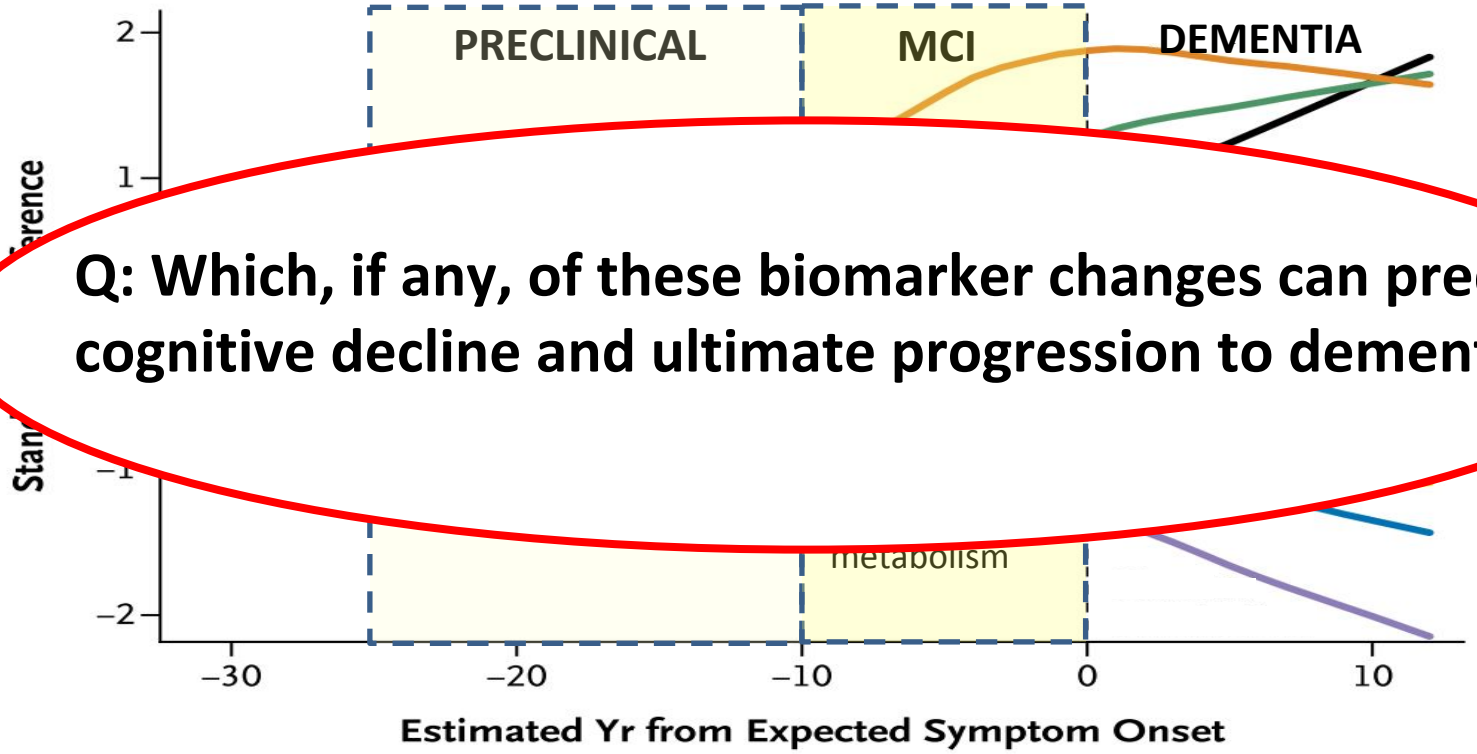
Proposed biomarker trajectories in Alzheimer's Disease



NIA-AA Preclinical Working

modified from Sperling et al., 2011, Alz & Dem

Time course of biomarker changes in the Dominantly Inherited Alzheimer Network (DIAN) study of autosomal dominant AD



Q: Which, if any, of these biomarker changes can predict cognitive decline and ultimate progression to dementia?

Bateman et al., NEJM, 2016

Useful CSF Markers…spoiler alert

Neuronal injury

- **Tau**… microtubule-associated protein
- (**P-tau**)… phosphorylated tau that makes up neurofibrillary tangles
- **VILIP-1**… visinin-like protein 1, neuronal calcium sensor protein
- **NRGN**… neurogranin, post-synaptic protein
- **SNAP-25**… synaptosomal associated protein-25, pre-synaptic protein

[NfL… neurofilament light chain]

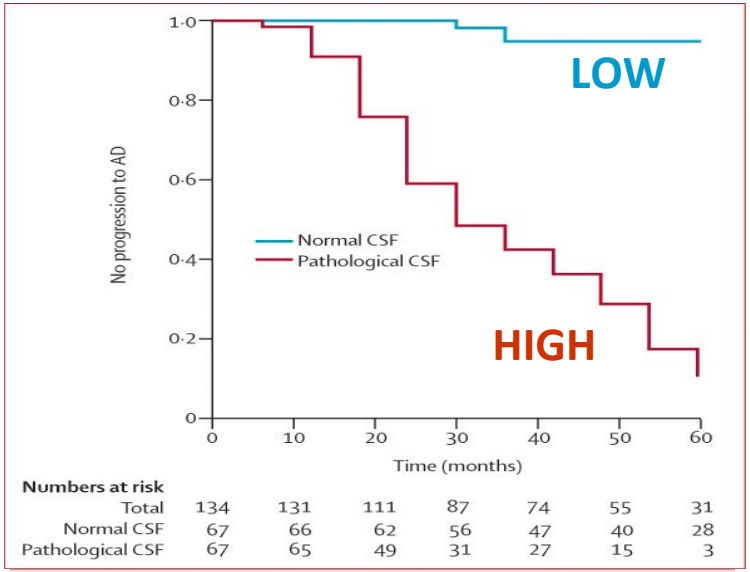
Neuroinflammation/gliosis

- **YKL-40**… aka, chitinase 3-like 1, astrocyte derived protein

… especially when consider amyloid status (amyloid-positivity or as ratio)

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

MCI →



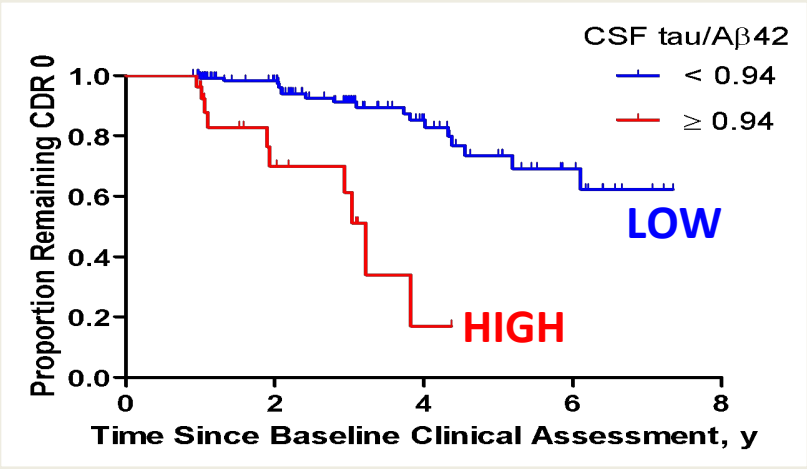
	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Pathological CSF (T-tau and Aβ42)	30·0 (9·32–96·8)†	17·7 (5·33–58·9)†
Pathological CSF (P-tau$_{181}$ and Aβ42)	26·3 (8·16–84·5)†	16·8 (5·02–56·5)†

N=134 MCI

Hansson et al., 2006, Lancet Neurol

HR 17.7 Tau/Aβ4
HR 16.8 P-tau181/Aβ42

Cognitively normal → MCI/AD



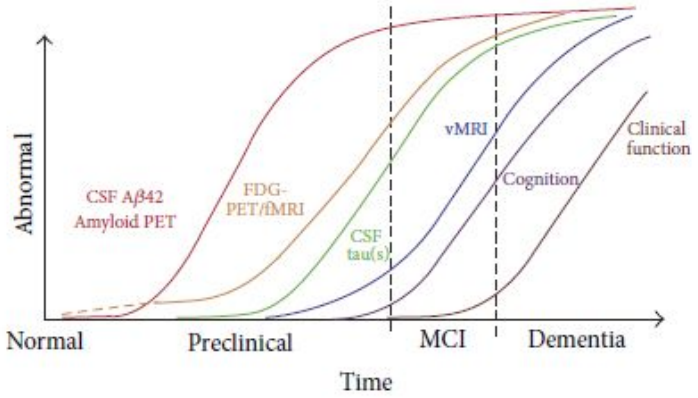
Upper 15% vs. lower 85% of values

(**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**
- *Craig-Schapiro et al., 2010, Biol Psychiatry*
- *Fagan et al., 2007, Arch Neurol*
- *Li et al., 2007, Neurology*

Proposed stages of preclinical AD as defined by biomarkers

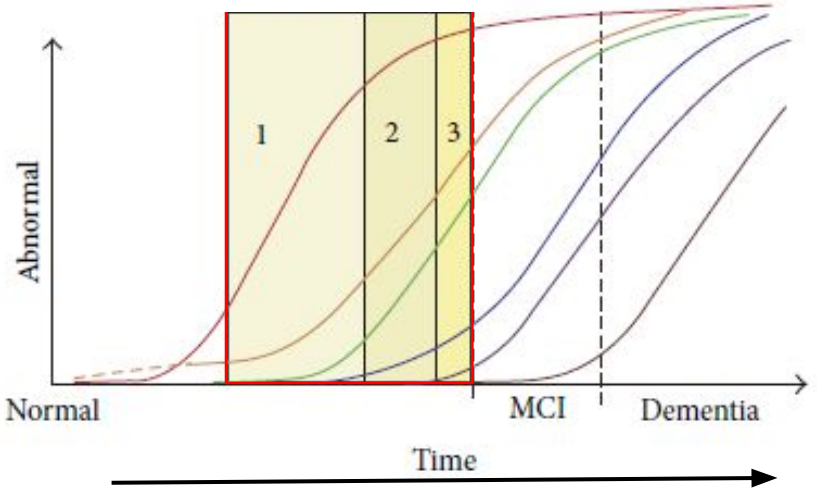


S1: amy+ injury-

S2: amy+ injury+

S3: amy+ injury+ subtle cog+

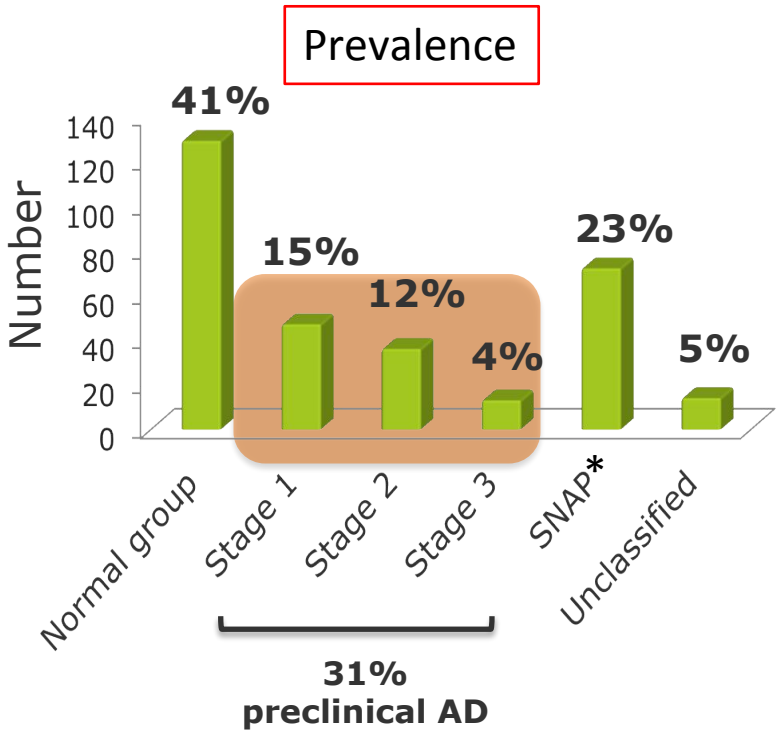
Preclinical Stages

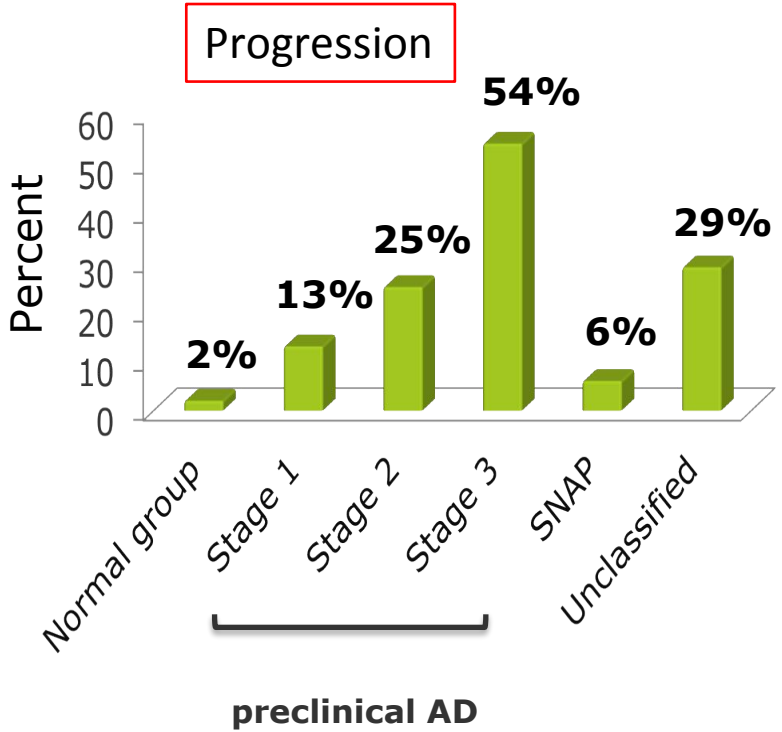


modified from Sperling et al., 2011, Alz & Dem

Prevalence of preclinical AD stages and progression to symptomatic AD within 5 years

N=311 cognitively normal (≥65yo)





*SNAP: amy- injury+

from Vos et al, 2013, Lancet Neurol

CSF VILIP-1 is a novel biomarker of neuronal injury and/or death

- CSF VILIP-1 levels are elevated in:
  - ✓ Acute stroke (Laterza et al., 2006, Clin Chem)
  - ✓ AD and other neurodegenerative disorders to a lesser degree (e.g., vascular dementia, VaD)
  - ✓ MCI/very mild AD

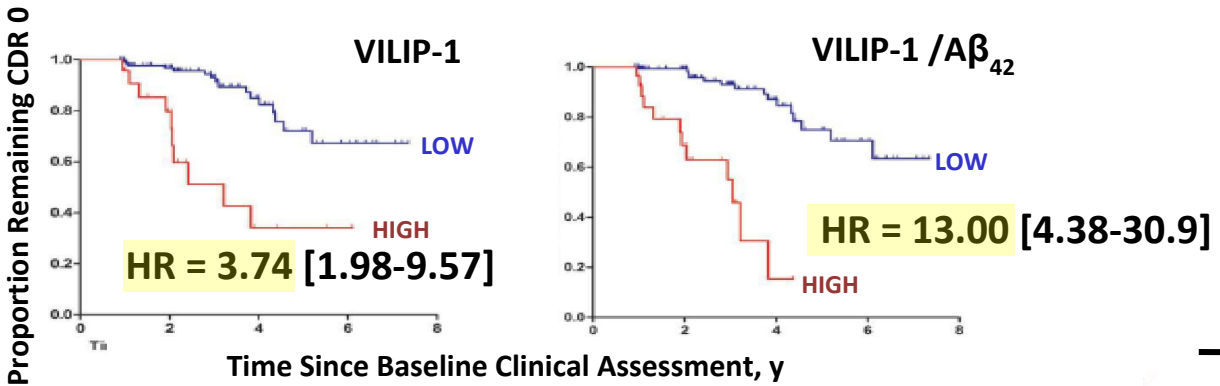
- CSF levels of VILIP-1 are positively correlated with:
  - ✓ CSF tau and ptau181
  - ✓ Hippocampal and whole brain atrophy

- High levels of CSF VILIP-1 predict:
  - ✓ Cognitive decline in cognitively normal individuals and those with MCI/very mild AD (especially when combined with CSF $A\beta_{42}$)

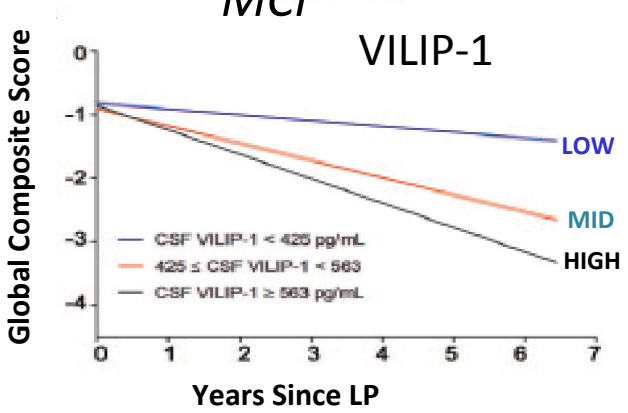
Lee et al., 2008, Clin Chem
Tarawneh et al., 2011, Ann Neurol
Tarawneh et al., 2013, Neurology

Kester et al., 2015, Alz Res Ther
Mroczko et al., 2015, J Alz Dis
Leko et al., 2016, J Alz Dis

CSF VILIP-1 as predictor of clinical progression in cognitively normal individuals (CDR 0 to CDR >0)…



…and in MCI



Tarawneh et al., 2011, Ann Neurol; Tarawneh et al., 2012, Neurology; (Leko et al., 2016, J Alz Dis)

Novel biomarkers of synaptic dysfunction and/or loss

- Synapse loss is a prominent and relatively early feature of AD. *(Davies et al., 1987; DeKosky & Scheff, 1990; Terry et al., 1991; Scheff & Price, 2003)*

- Cognitive decline correlates more strongly with synaptic loss than plaque or tangle pathology. *(Davies et al., 1987; Terry et al., 1991; Sze et al., 1997; Coleman & Yao, 2003; Scheff et al., 2007)*

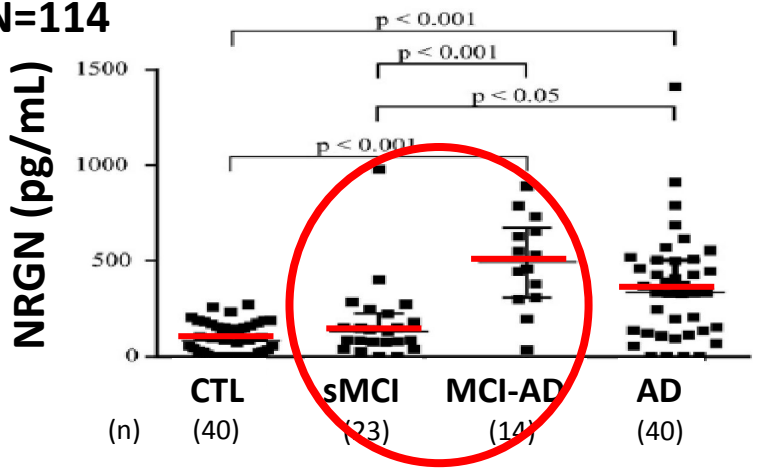
- Levels of synapse-associated proteins are reduced in AD brain. *(Davidsson & Blennow, 1998; Reddy et al., 2005; Beeri et al., 2012)*

- Synapse-associated proteins can be measured in the CSF and are now being evaluated as potential biomarkers in AD.

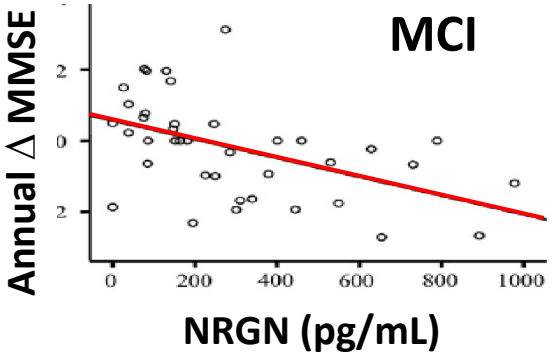
  - Neurogranin (NRGN) (post-synaptic)

CSF NRGN levels are higher in AD vs controls and in those who progressed from MCI to AD vs those who remained MCI (sMCI)

N=114

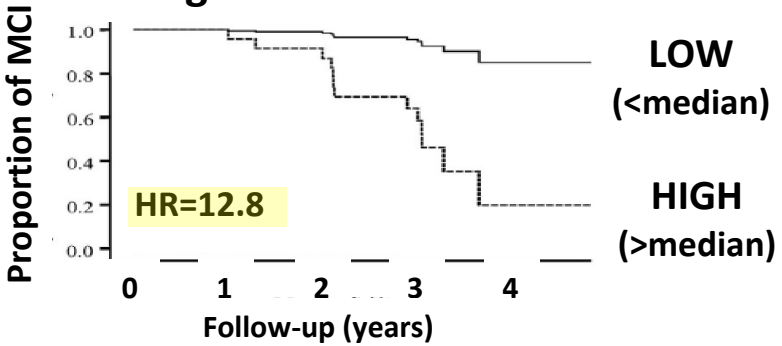


CSF NRGN and change in MMSE



Baseline CSF NRGN is associated with cognitive decline (change in MMSE) in MCI (n=37)

Progression from MCI to AD



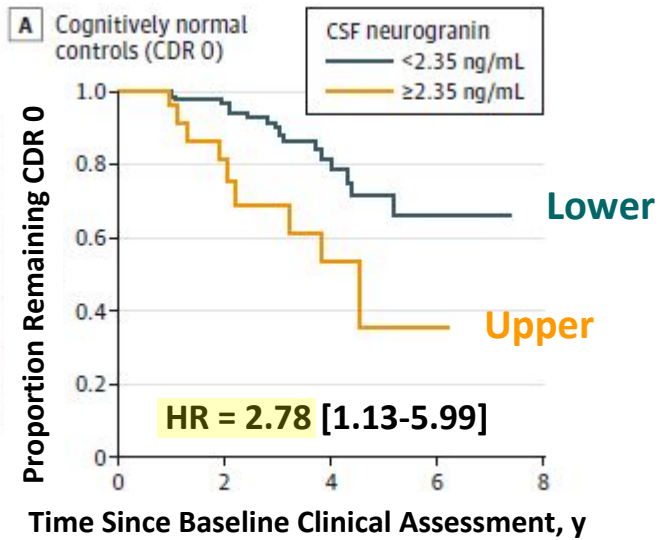
High CSF NRGN (>median) predicts progression from MCI to AD (HR=12.8, [1.6-103.0])

Kvartsberg et al., 2015, Alz & Dem

Kester et al., 2015, JAMA Neurol; Portelius et al., 2015, Brain; Mattsson et al., 2016, EMBO Mol Med

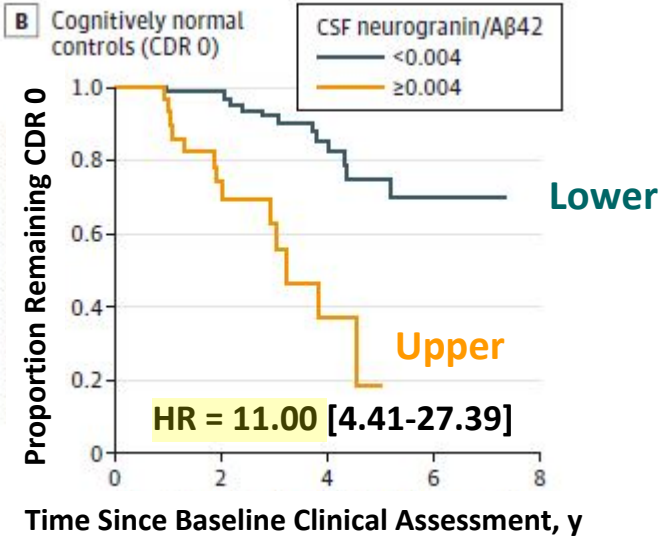
Higher levels of CSF NRGN (and the ratio of NRGN/Aβ42) predict progression from cognitive normality (CDR 0) to cognitive abnormality (CDR >0)

NRGN



Tau HR = 2.75 [1.31-6.97]

NRGN/Aβ42

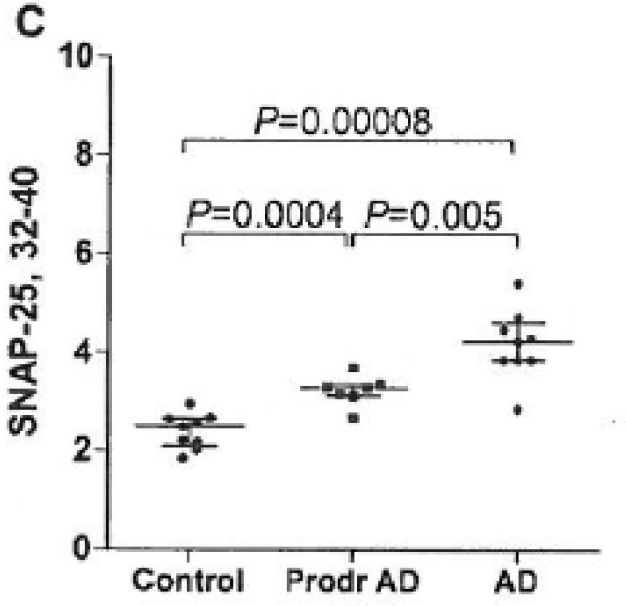


Tau/Aβ42 HR = 9.82 [3.11-21.28]

- N=302, mean age 73
- Biomarker dichotomization at 85th percentile

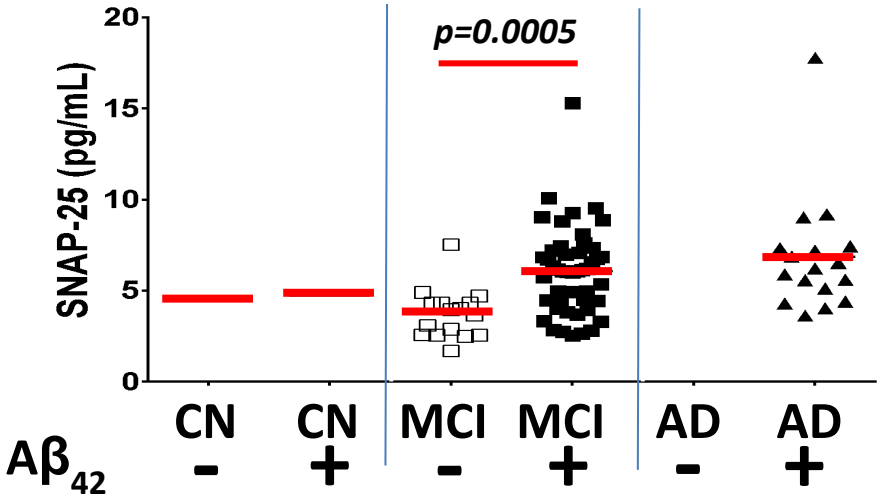
Tarawneh et al., 2016, JAMA Neurol

CSF SNAP-25 levels are higher in AD and prodromal AD compared to controls…



Brinkmalm et al., 2014, Mol Neurodegen

…and in amyloid-positive individuals with MCI



(Amyloid+, CSF $A\beta_{42}$<192pg/mL)

Sutphen et al., 2016, AAIC conference

CSF YKL-40 is a novel biomarker of neuroinflammation/gliosis

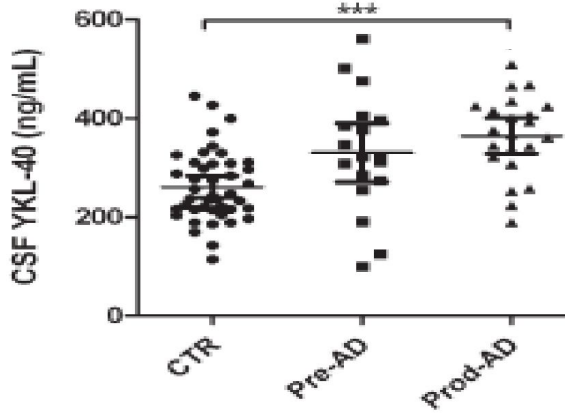
In the brain, YKL-40 (aka, chitinase 3-like 1) is an astrocyte-derived glycoprotein that may play a role in neuroinflammation and/or remodeling.

- CSF YKL-40 levels increase with age (*Antonell et al., 2014, J Alz Dis; Sutphen et al., 2015, JAMA Neurol)*

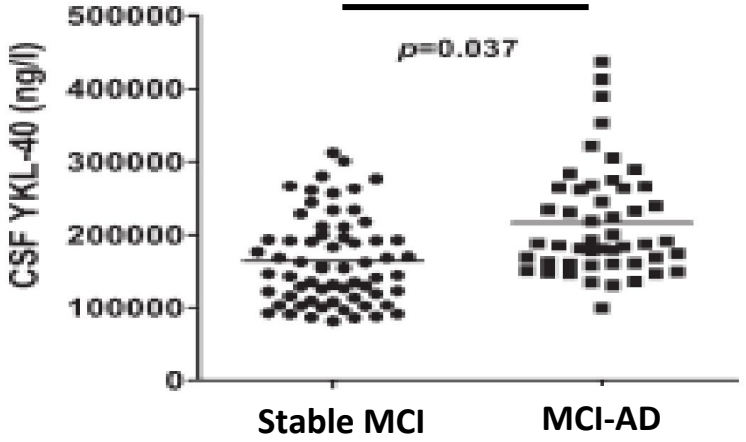
- CSF YKL-40 levels are elevated in:
  - Purulent Meningitis *(Ostergaard et al, 2002, Clin Diagn Lab Immunol)*
  - Traumatic Brain Injury *(Bonneh-Barkey et al., 2010, J Neurotrauma)*
  - Multiple Sclerosis (MS) and decreases with immunosuppressive treatment *(Malmestrom et al., 2014, J Neuroimmunol)*
  - AD and in preclinical AD/MCI cohorts that progress to AD dementia *(Craig-Schapiro et al., 2010, Biol Psychiatry; Olsson et al., 2013, J Alz Dis; Kvartsberg et al., 2015, Alz & Dem; Kester et al., 2015, Alz Res Ther)*

- High levels of CSF YKL-40 predict:
  - Cognitive decline MCI and in cognitively normal individuals (especially when combined with CSF $A\beta_{42}$) *(Craig-Schapiro et al., 2010, Biol Psychiatry; Olsson et al., 2013, J Alz Dis; Kester et al., 2015 Alz Res Ther; Hellwig et al., 2015, Alz Res Ther)*

Levels of CSF YKL-40 are elevated in "prodromal AD" and in individuals with MCI who progress to AD dementia

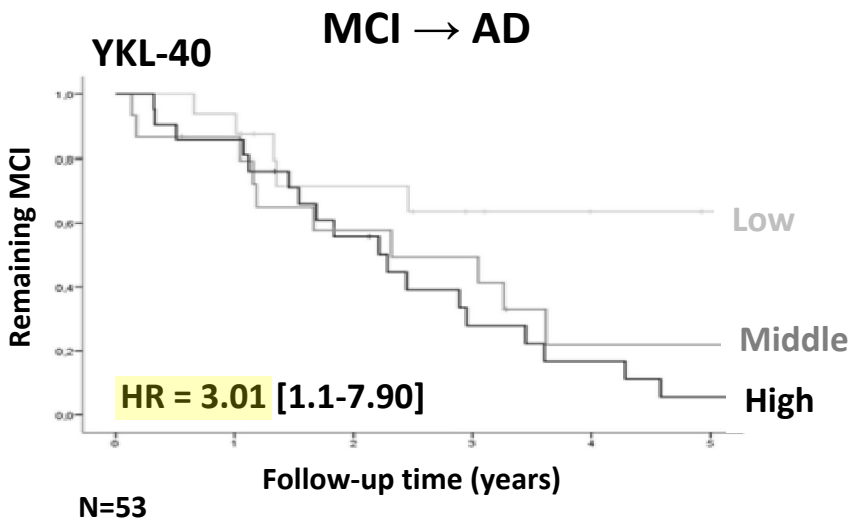


Antonell et al., 2014, J Alz Dis

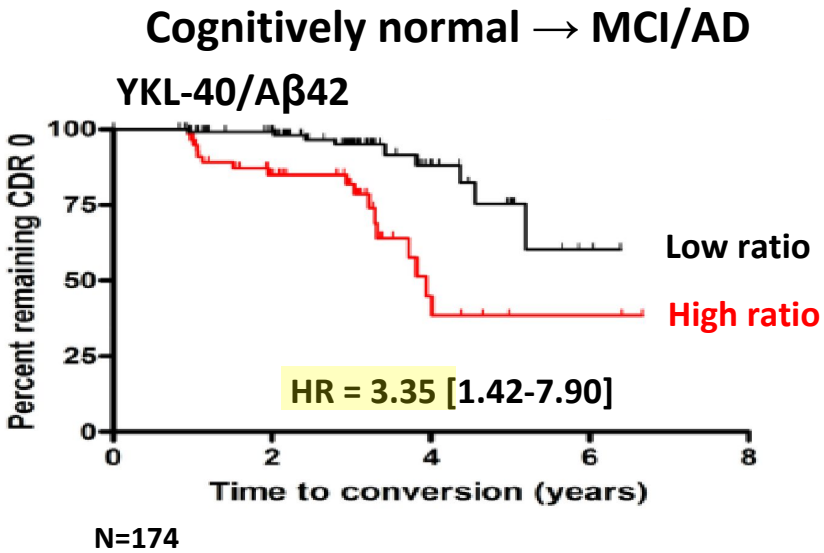


Olsson et al., 2013, J Alz Dis

High CSF YKL-40 predicts progression from MCI to AD and from cognitive normality to cognitive abnormality (CDR 0 to CDR>0), especially when combined with CSF Aβ$_{42}$



Kester et al., 2015, Alz Res Ther



Craig-Schapiro et al., 2010, Biol Psychiatry

Summary and Points of Discussion…

1) Higher levels of CSF markers of neuronal injury, including tau, VILIP-1, NRGN and SNAP-25 are observed in individuals with MCI who later progress to AD compared to those who remain MCI.
2) Higher levels of these markers predict cognitive decline and progression to dementia in individuals with MCI, as well as in cognitively normal individuals in the preclinical stages of AD (amyloid +).

Points of discussion…

3) Are these novel markers useful beyond what is currently being evaluated with tau (and ptau)?
4) Might they display differential utility along the temporal course of the disease?
5) Is there any specificity of these markers for AD compared to other neurodegenerative disorders?
6) Might markers of synaptic dysfunction/loss be the most sensitive predictor of cognitive decline in the earliest (prodromal/preclinical) disease stages?
7) Will synaptic and/or injury biomarker profiles be useful for tracking cognitive performance in clinical trials (and eventually in clinical practice)?
8) Can synaptic and/or injury markers be used as surrogate outcome measures in clinical trials?
9) Might non-tau markers providing alternate neuronal injury markers in clinical trials targeting tau-specific processes (e.g., anti-tau antibodies)?

Acknowledgements

And especially all research participants and their families!